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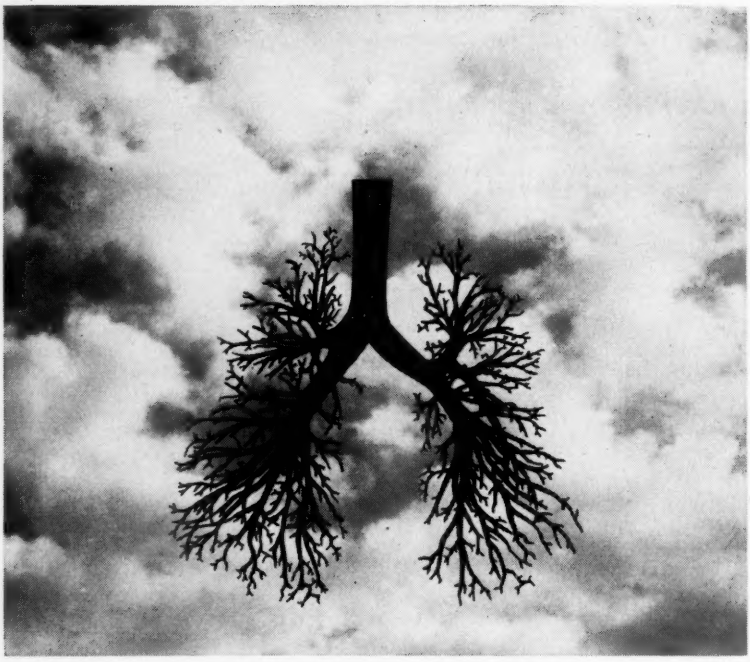

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ARSENIC IN THE TREATMENT OF ASTHMA

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THE TREATMENT of a chronic illness, in this instance asthma, makes use of many varied compounds and procedures. These include the blatantly advertised "asthma cures," which cause so much misunderstanding and hardship to asthma sufferers.

This paper concerns the role of inorganic arsenic in the treatment of asthma. Arsenic, at one time an important tool of professional poisoners, has been used as a therapeutic agent for many centuries. Arsenic, mercury, antimony formed a popular therapeutic trilogy. The toxic effects of mercury were overt and soon recognized, consisting of salivation, gum injury and, finally, loss of the teeth. Antimony was employed mainly as a cosmetic base. The toxic effects of arsenic, particularly of the inorganic form, were found to be very insidious, and even to this day these toxic effects are not always clearly remembered and promptly recognized.

It has been known for thousands of years that the repeated administration of small amounts of arsenic will soon lead to a tolerance of this drug so that massive doses of inorganic arsenic will be tolerated. However, we are now concerned mainly with the effects of small, "therapeutic" doses of this chemical on the human system.

Inorganic arsenic is absorbed promptly through the gastrointestinal tract, through the skin when applied in the form of ointments, and through the mucous membranes. When inorganic arsenic has been absorbed it is lodged in the cells of the skin, hair, nails and other epithelial tissues. In these cells it attaches itself firmly to a protein. To a lesser degree, in-

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organic arsenic seeks out the endothelial tissue, particularly in the liver, kidney and central nervous system.

The attachment of inorganic arsenic with the protein in the epithelial and endothelial cells is firm, and the excretion of inorganic arsenic is therefore extremely slow and always incomplete. It has been reported that the presence of inorganic arsenic can be demonstrated in the human skin, hair, and nails many years after it has been ingested. Some chemists presume that the fixation of inorganic arsenic in these tissue cells is so firm that its presence can be detected many years after the inorganic arsenic recipient has died and until all the tissues concerned have been completely destroyed.

Organic arsenic, on the other hand, is more loosely bound. A study conducted by our Department of Biochemistry on many patients who received organic arsenicals for the treatment of syphilis showed that the presence of organic arsenic could not be demonstrated by the usual biochemical methods eight to twelve months after the injection of an arsenical compound.

Furthermore, organic arsenic will not be deposited in the hair, skin or nails in a protein fixed form, except after prolonged use of such a drug. The only exceptions to this were the few patients who developed a severe arsenical dermatitis or hepatitis following the administration of arsphenamine or neophenamine.

The normal person excretes 0 to 0.05 mgms of arsenic in the urine over a twenty-four-hour period. These figures are based on a study of over a hundred medical students of this school under the direction of Dr. Haywood Taylor. Patients treated with organic arsenicals will excrete abnormal amounts of arsenic in the urine not longer than four months after the last administration.

The deposition of inorganic arsenic in the epithelial cells produces various histologic changes. In the skin these changes invite hyperplasia which results in keratosis, or the reaction leads to atrophic dermal changes. An acute inflammatory response is rarely observed. The resulting skin lesions occur commonly across the knuckles and toe joints, the ankles, the extensor surfaces of the extremities and very rarely on the face. They seem to occur where the superficial vascular bed is less abundant. In many respects, the distribution of these skin lesions stimulate those seen in psoriasis. Frequently, patients who have received inorganic arsenic over a prolonged period of time develop warty, hyperplastic lesions on the palms of the hands and soles of the feet. Unfortunately, a good percentage of these lesions become malignant after months or years. Such skin eruptions have been described in individuals who received their last dose of inorganic arsenic ten to fifteen years previously. These warty and hyperplastic lesions may become cancerous soon after they appear.

The mucous membranes, the liver, kidneys and other tissues rich in endothelial cells do not react to this injury in a manner which can be consid-

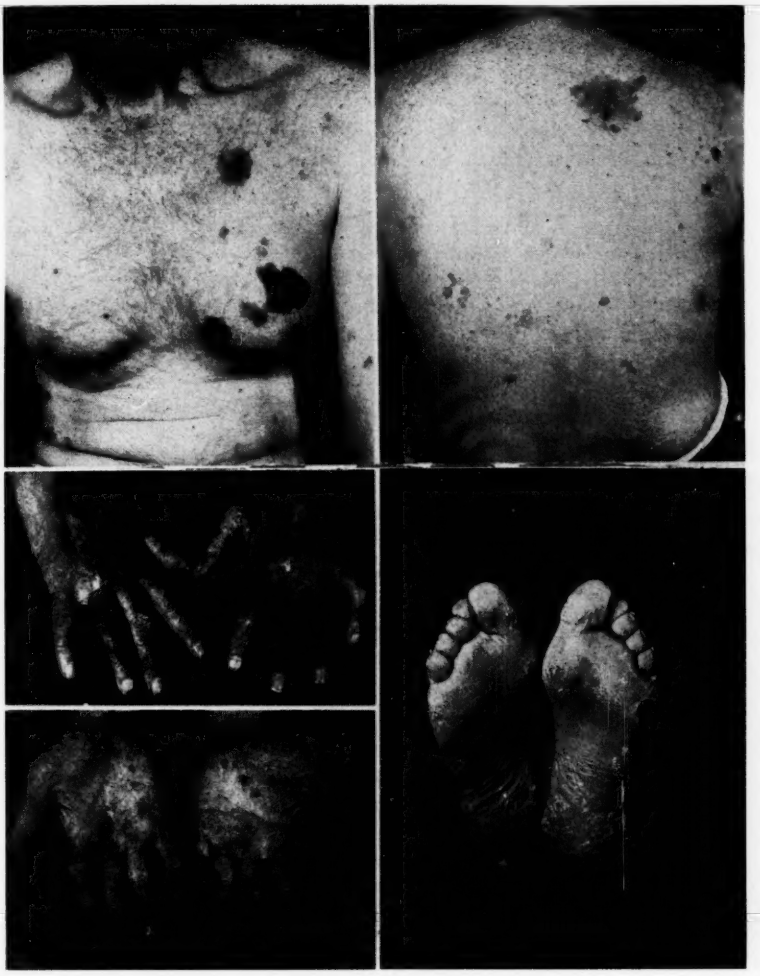

Fig. 1. Note the hyperkeratotic plaques on the front and back of the trunk, also the keratodermia. Similar lesions are seen on the dorsum of the hands. The lesions on the soles of the feet have a tendency to form verrucae. The patient took inorganic arsenic as Fowler's Solution for a period of a year and a half, five drops three times a day with potassium iodide. These lesions appeared eight years after he had stopped taking Fowler's Solution.

ered "characteristic" of an intoxication with inorganic arsenic. The injury of the endothelial system can then be attributed to inorganic arsenic only by a careful analysis of the patient's history and the presence of the skin lesions described, if the biochemical studies are, at least, suggestive. If

TABLE I.

No. Pts.	Age		Sex		Duration of "Gay Treatment"				Interval Before Visit to Duke Hospital		
	Youngest	Oldest	M	F	2 Wks. or Less	4-6 Wks.	1-1½ Yrs.	2-3 Yrs.	2-6 Mos.	1-2 Yrs.	2-3 Yrs.
4	33	62	4	0	4	0	0	0	4	0	0
5	32	65	4	1	0	4M+1F	0	0	2M+1F	1	1
4	47	63	2	2	0	0	1M+2F	1	2M	1F	1F
4	61	65	2	2	0	0	2M+2F	0	1F	2	1F
Total 17			12	5					10	4	3

the patient presents also a severe leukopenia or thrombocytopenia indicative of bone marrow distress, the diagnosis of endothelial damage due to inorganic arsenic becomes more tenable.

MATERIAL STUDIED

This report is based on an observation of seventeen adult patients, ranging in age from thirty-two to sixty-five years. Of these, twelve were males and five were females. All were white patients. This is probably due, in part at least, to the fact that the treatment which uses inorganic arsenic, usually the "Gay Treatment," in our section of the country, is still quite expensive. The majority of the males were younger than the females and this can be explained by the greater urge of the working male to find a "cure" for his affliction. The individuals studied received this treatment over a period ranging from two weeks to two and one-half years. The time interval elapsed between the last administration of inorganic arsenic, a part of this treatment, until they came to Duke Hospital, ranged anywhere from three weeks to three years. All of these patients came to the Duke Hospital Clinic because the sought-for "cure" had not materialized. The following table shows the number of patients, their sex and age, the duration of their exposure to the "Gay Treatment," or a modified form of it, and the time interval between the last administration of the "Gay Treatment" and the visit to the Duke Hospital Clinic.

METHOD OF STUDY

Every patient received a complete allergy investigation comprising a thorough medical and allergy history; a minute physical examination and necessary peripheral blood studies; x-rays of the chest with fluoroscopy, including films to estimate the aeration of the lungs; the necessary intradermal skin tests; bacteriological studies of the sputum or nasopharyngeal secretions; the indicated nose and throat survey, and pulmonary function studies. In addition, they were subjected to biochemical investigations to determine their liver function and kidney function tests. In many instances, hair obtained from these patients, usually from the pubic region, was analyzed for arsenic. Finally, twenty-four-hour urine collections were ob-

tained on every patient and analyzed for their arsenic content. When indicated, a consulting dermatologist and neurologist examined the patient.

CASE REPORTS

The observations made on the seventeen patients are illustrated by the report of significant examples of the effect of inorganic arsenic on four individuals of this group.

Case 1. MINOR SKIN ERUPTION: MILD HEPATIC INJURY. R. A. was a man aged forty-two years with mild, non-seasonal allergic rhinitis of twenty years' duration. Marked susceptibility to head and chest colds had been shown since childhood. Onset of asthma came fifteen months before visit to Duke Hospital. There was no previous allergy survey, desensitizing or vaccine therapy. Family history was negative for the common allergic disorders and the collagen diseases.

The clinical impression was: recurrent tracheobronchitis; allergic rhinitis; asthma, mainly of the intrinsic type, and moderately severe obstructive emphysema.

The accessory findings were: a normal peripheral blood picture except for 8 per cent PME; a sputum loaded with Gram-positive cocci and diplococci in clumps and chains, a normal urine and blood serology.

X-ray studies of the chest showed a marked emphysema. Contrast films, as well as a fluoroscopic examination, disclosed low, flat diaphragms and poor aeration of the lung fields. The pulmonary function studies (carried out by Dr. Hickam of the Cardiopulmonary Laboratory) were reported as "ventilation restriction and insufficiency compatible with pulmonary emphysema and fibrosis."

The EKG and complete otolaryngologic examinations were essentially negative.

Intradermal skin tests to 155 common allergens gave positive reactions to timothy grass, short ragweed, house dust, hormodendrum, fusarium, oidomycin.

Aerobic and anaerobic cultures of the sputum yielded: H. staphylococcus aureus, H. streptococcus, N. flava and a mixture of anaerobic bacteria.

This patient received inorganic arsenic in the form of Fowler's solution, twenty to twenty-eight drops three times a day in conjunction with aminophylline, K.I. for two weeks; then cortisone, ACTH, and, finally, increasing doses of adrenaline, subcutaneously and intramuscularly. He was taking cortisone, 100 mgms a day, when he came to Duke Hospital two and one-half weeks later.

On admission he was in "status asthmaticus." The skin was dry and there was a slight increase in pigmentation, over the knuckles, knees, shins and elbows. An interesting finding was an acute conjunctivitis of the left eye with edema of the soft tissues.

His *urine arsenic* in twenty-four hours was 2.0 mgm, which is almost one hundred times the normal. The liver function tests showed as the only abnormality a 5 per cent retention of bromsulphaline in forty-five hours. The kidney function tests were normal.

The patient was taken off cortisone within six days, responded nicely to the usual anti-asthmatic remedies and left the hospital eighteen days after admission, symptom-free.

Case 2.—SEVERE MACULO-PAPULAR SKIN ERUPTION. NO EVIDENCE OF HEPATIC DISEASE. R. M. C. is a woman aged fifty-six years; Duke No. A-10316. She gave a history of recurrent attacks of bronchitis, often followed by asthma, since the age of thirty years. Furthermore, she had suffered from seasonal (autumnal) hay fever since the age of thirteen years. A marked susceptibility to head and chest colds ensued; finally, the attacks of asthma became her main concern; with age her

exertional dyspnea increased. Her previous personal history and her familial history were negative for the common allergic disorders.

She was thin, orthopneic and dyspneic when examined in January 1954. She had an extensive maculopapular, erythematous eruption over the dorsum of the feet, about the ankles, over the knuckles and on the elbows; in these areas the skin was dry and almost lichenified and darkly pigmented. Fissures and vesicles were absent. The nails were not remarkable (no ingestion of inorganic arsenic in three years). The chest was emphysematous, the lateral expansion increased, the diaphragms low, the breath sounds distant and obscured by inspiratory musical râles. The heart was normal; the blood pressure 120/86; the rest of the examination was not remarkable.

The hemoglobin, hematocrit, and WBC count were normal, but there were 12 per cent PME. The blood serology, urine, and stool were normal. The blood electrolytes, kidney function tests and other biochemical studies, including the liver function tests, were normal.

The EKG was normal. The fluoroscopic and x-ray studies of the lungs revealed emphysema. Pulmonary function studies were not done.

The intradermal skin tests yielded positive reactions to a number of common pollens, inhalants and fungi.

Sputum culture yielded N. flava, N. sicca, S. viridans and a mixture of anaerobic bacteria.

The patient had taken the "Gay treatment" for one and one-half years and she returned to Duke Hospital two years later because she had not been benefited; she had tried various other "asthma cures" in the interim. Her urine arsenic at this time was entirely negative. The pubic hair still gave a strong positive test for arsenic. The dermatitis had subsided considerably.

The patient was again instructed in the accepted antiasthmatic regime, the use of antispasmodics, in breathing exercises to counteract the handicaps of emphysema, and started again on a systematic course of desensitizing and autogenous vaccine treatments. This patient suffers from many psycho-physiological manifestations which pose an added problem. However, when she was last seen in the Clinic, five months ago (four months after she left the hospital), she seemed happier, had gained more insight into her problems and had ceased to hunt for a "quick cure."

This is an example of a rather severe, generalized dermatitis occurring one to three years after the ingestion of inorganic arsenic.

Case 3.—Severe Chronic and Recurrent Nasal Obstruction since age fifteen, culminating in bilateral Caldwell-Luc operation seventeen years later; Recurrent Tracheobronchitis and Asthma beginning at age of twenty-two years. Weakness, Vertigo, Severe Bouts of Nausea and Vomiting. L. M. L. is a white woman aged thirty-two years, Duke No. B-30326. No history of eczema, urticaria or food or drug intolerance was given. Recurrent bouts of severe nasal obstruction, mild sneezing, purulent nasal discharge, non-seasonal, beginning at the age of fifteen years, had been experienced. She was treated by nasal "washings and irrigations," nasal packings with argyrol on many occasions. Frequent bouts of tracheobronchitis accompanied by a paroxysmal cough productive of "yellowish or greenish" sputum from the age of twenty-two years on, soon culminating in non-seasonal, severe asthma. Tonsillectomy and adenoidectomy had been done at the age of seven years. Bilateral Caldwell-Luc operation at the age of thirty-two years. Family history essentially negative for the allergic disorders.

Treated at the Gay Clinic in Biloxi, Miss., beginning one and one-half years before last visit to Duke Hospital and was taking the prescribed solution when she entered this hospital.

She was a well developed and well nourished woman who was in marked respi-

ratory distress, orthopneic and dyspneic, moderately cyanotic and afebrile. There was a purulent nasal discharge. The chest was normal in contour but the expansion was markedly limited. The diaphragms were normal in position and moved well. The breath sounds were obscured by generalized inspiratory and expiratory dry, musical râles. The heart was normal except for a tachycardia. The blood pressure was 110/88. The rest of the examination was not remarkable.

The blood hemoglobin and hematocrit were normal. The WBC on admission was 12,400 and the differential white cell formula showed 9 per cent eosinophils. The blood serology was negative. The urine was normal. A complete liver profile and kidney function tests failed to disclose any abnormalities.

The EKG and EEG were normal. X-ray and fluoroscopy of the chest were essentially normal on the third hospital day, when the patient had responded to the usual antiasthmatic measures.

Sputum examination with the Gram stain showed many Gram-positive cocci in pairs, chains, clumps and a few Gram-negative rods and bacilli. Acid fast stains were negative.

Sputum cultures yielded alpha and beta hemolytic streptococci, N. flava, S. albus, and a mixture of anaerobic bacteria.

Intradermal skin tests to 152 common pollens, other inhalants, foods and fungi were negative.

The twenty-four-hour urine arsenic was 0.18 mgms. Since this was such a high content, the pubic hair arsenic was not determined.

During the first ten days in the hospital the patient complained bitterly of "dizziness," weakness, nausea and vomited frequently. She denied headache, visual and auditory disturbances. There was no apparent abnormality of the senses of smell and taste. She also denied paraesthesiae. The neurological survey was entirely normal. The asthmatic seizures ceased within three days after the use of the usual antispasmodics. The weakness, nausea, vomiting and dizziness gradually subsided after omitting all oral feeding and medications. At no time did she develop diarrhea; the stool examinations showed nothing strikingly abnormal.

The patient left the hospital after three weeks in good condition. The twenty-four-hour urine arsenic one week before discharge was still elevated (0.10 mgms).

The patient was instructed to discontinue the use of inorganic arsenic. She was started on autogenous vaccine treatments and oral medications as needed. When last seen in January of this year she was doing well.

Case 4.—Severe Chronic and Recurrent Skin Lesions. Severe Hepatic Damage with Hepatic Failure. Renal Insufficiency. A. D., a woman, aged sixty-five years, Duke No. 51789. She had an allergic rhinitis, worse in the fall, beginning in childhood. Her asthma started at the age of twenty-eight years and was not seasonal. She developed an increasing susceptibility to chest colds, usually accompanied or followed by asthma. Because of her occupation as a circus trapeze artist, she did not find the opportunity to have the proper medical care. After marriage, the rhinitis and asthma improved; she ascribed this to a more orderly life and hoped to outgrow her allergies. When this did not materialize, she began to seek various advertised "asthma cures."

Her past personal history was otherwise negative for allergy. Her familial history could not be ascertained.

After her first visit to the Duke Hospital Clinic it became apparent that she expected a "quick and permanent cure." Since this could not be promised to her, she visited a clinic in a nearby town where she received the "Gay Treatment."

Her family physician estimated that she took the solution containing inorganic

arsenic, off and on, for about one and one-half to two years. About two months after she discontinued this treatment, she became very ill, had severe nausea and vomiting, diarrhea, became jaundiced and then developed generalized anasarca. She complained of a recurrent, at times pruritic, erythematous, scaling eruption involving the trunk, extremities (extensor surfaces), which appeared eight weeks after she began the "Gay Treatment."

Her urine, skin and hair arsenic content were not determined at that time. The B.S.P. test showed 20 per cent retention of the dye after forty-five minutes; the plasma proteins were: Albumin 2.5 gms., Globulin 3.0 gms., with a reversed A/G ratio. The urine contained a large amount of albumin and in the sediment there were many hyaline and granular casts. No other laboratory determinations were done.

There had been a transitory amelioration of her bronchospasm. The patient gradually improved as far as the liver and kidney damage were concerned. However, the episodes of asthma, the paroxysms of cough, the exertional dyspnea gradually grew worse. She became increasingly weaker and soon began to complain of irritability and inability to concentrate. Reading and sewing became very difficult.

The patient was readmitted to Duke Hospital about three years after she had discontinued the "Gay Treatment." She was large framed, somewhat overweight, afebrile, emotionally unstable, quite orthopneic and dyspneic and also harrassed by a paroxysmal, dry cough, accompanied by wheezing. The skin was dry and hyperkeratotic plaques were present on the palms of the hands and soles of the feet. There was an indistinct lichenification and pigmentation across the knuckles, dorsum of the feet and about the ankles; three spider angiomata were present on the neck and chest. There was no jaundice. The chest was emphysematous, the lateral expansion was almost nil, the diaphragms quite low and fixed, the breath sounds distant and obscured by inspiratory and expiratory musical râles. The heart was enlarged; A_2 was greater than P_2, and there was a systolic gallop present. The peripheral arteries and retinal arteries were tortuous; the blood pressure was 180/110. There were no exudates in the ocular fundi. The abdomen was distended. The liver was moderately enlarged and tender. The tip of the spleen was barely palpable in the left axillary line on deep inspiration. A moderate ascites was demonstrated.

The peripheral blood picture was normal. The serology was negative. Urine examination showed the persistent presence of protein (1+ to 2+), a specific gravity which ranged from 1.003 to 1.009, and many hyaline, some granular and occasional waxy casts. Red and white blood cells were rarely seen. The benzidine reaction was negative; the stool specimens gave occasionally a positive reaction with the Guaiac reagent.

X-ray studies of the chest again disclosed marked emphysema with low diaphragms, and poor aeration of the lung fields. The heart was enlarged to the left, the aorta tortuous.

The EKG showed a left axis deviation, a right bundle branch block (she had been taking digitalis) and non-diagnostic T wave changes.

The plasma proteins were 5.5 with an A/G ratio of 1.0. The thymol turbidity, flocculation and the Van denBergh were normal. The prothrombin time was 70 per cent of normal; the alkaline phosphatase was normal; the serum cholesterol was 330 mgms per cent. The B.S.P. showed 35 per cent retention of the dye after thirty minutes and 10 per cent retention after forty-five minutes.

The P.S.P. test was abnormal with a total excretion of 40 per cent in two hours.

The patient responded to the usual antiasthmatic regime while in the hospital. She was also restricted to a low sodium diet. After she left the hospital, she again refused to follow a strict regime, became increasingly dependent on narcotics and died suddenly eight months after discharge. An autopsy permit was not obtained.

DISCUSSION

Any therapeutic procedure must be subjected to close scrutiny. This entails not only a clinical appraisal of the efficacy of the therapeutic measure, but also of the reason on which such a therapeutic procedure is based. It is most important, of course, to be aware of any dangers which it engenders. Those who are concerned with allergy must be particularly aware of this, not only during the study of a patient,[2] but also when his treatment is planned. This applies particularly to the management of an asthmatic.[7,8,13]

During the last five years, the use of inorganic arsenic, and particularly as part of the "Gay Treatment" has been the subject of several articles in the medical literature. The Letters of the International Correspondence Society of Allergists contain several communications by reputable men from different localities of the U.S.A., expressing their approval or disapproval of the "Gay Treatment."[11]

The "Gay Formula" has been reported as follows:*

	Adults	*Children*
Fowler's solution	8.0 cc	5.0 cc
Potassium Iodide (sat. sol.)	6.5 gms.	4.0 gms.
Phenobarbital	0.6 gms.	0.12 gms.
Saccharin	0.5 gms.	0.06 gms.
Tincture of Cudbear	1.0 cc	
Distilled water to make a total of	60.0 cc	same
Sig. one teaspoonful twice daily		same or two teaspoonfuls

Arsenical dermatitis has been recognized for many years. The reintroduction of Fowler's solution for the treatment of polycythemia and the chronic leukemias, especially of the lymphocytic type,[4] reawakened our interest in this dermatological complication.

A New York physician reported recently an asthmatic who developed a dermatitis pigmentosa about eight months after taking the Biloxi Formula for fifteen months (twenty-five bottles of four ounces each). The skin eruption was preceded by a period of anorexia, occasional diarrhea which began three weeks after he started the treatment. The patient didn't react to a patch test of Fowler's solution or to the compound formula ("red liquid"). His urine arsenic was 0.7 mgm per cent. Another patient developed an arsenical pigmentation of the skin and diffuse arsenical keratodermia of the palms and soles and trunk "several months" after he had taken the arsenic-containing medication, two teaspoonfuls daily for fifteen months.[10]

Three of the four patients reported here had skin lesions. These varied

*This is not intended to represent the exact "Gay Formula"; there are undoubtedly several variations of this compound which are used in different sections of this country.

from a mild and transient erythrodermia to an irreversible hyperkeratosis involving mainly the extensor surfaces of the extremities and the soles of the feet and palms of the hands. Changes in the nails were not conspicuous at the time the patients were examined. (Cases 1, 2 and 4). Of the remaining thirteen patients, eight gave a history of a transient skin eruption, usually described as "dryness and itching"; another complained of a recurrent urticaria consisting of "very small whelps," and only mildly pruritic with occasional swelling of the lips an eyelids. The other four patients did not have skin eruptions. When these thirteen patients were examined, five showed a mild hyperkeratosis and pigmentation on the shins, knuckles and elbows. These skin changes would probably have been missed if they had not been specifically searched for.

Dr. Susan Dees, in charge of our Pediatric Allergy Clinic, states that she has seen eight or ten children who presented a slight keratosis on the extensor surfaces of the extremities; she felt that the most striking finding, however, was a hyperpigmentation in the axillae, groins, elbow and knee hollows which suggested the pigmentation seen in Addison's disease. These were, of course, all children who had received inorganic arsenic.[3] It was her impression that she must have missed at least another ten children who showed similar skin changes before she began to look for them, in those who had received a medication containing inorganic arsenic.

It is obvious then that injury to the skin is common in individuals who receive inorganic arsenic over an extended period of time. The time of exposure to inorganic arsenic is obviously important and is reflected in direct proportion by the severity of the cutaneous alterations.

Some patients develop biochemical or clinical evidences of hepatic disease. There are many reports of liver injury due to organic arsenic, particularly during the era when the arsphenamine compounds were the mainstay of antisyphilitic treatment. More recently, scattered instances have been reported of patients who developed liver disease after the prolonged administration of Fowler's solution, and other compounds containing inorganic arsenic.[12] As a cacodylate, inorganic arsenic has been used extensively in Europe and South America for many years and for many purposes. As Fowler's Solution, or as a part of many other formulas, inorganic arsenic has been used extensively in this country. It is surprising, therefore, that not only the American medical literature, but also the foreign literature has so few articles dealing with the injurious effects of inorganic arsenic upon the human body.

Two of the patients described in detail suffered from mild (Case 1) or severe liver damage (Case 4). Of the remaining thirteen patients, only two others had biochemical tests which suggested liver insufficiency. It is well known that such biochemical abnormalities or their absence, are not an accurate measure of the histologic or functional integrity of the liver.

Only one patient (Case 4), out of seventeen, showed clinical and labora-

tory evidences of renal damage. In this woman it is impossible to ascribe the injury, unqualifiedly, to the prolonged intake of inorganic arsenic. She suffered from hypertensive cardiovascular disease and died of a coronary accident. An autopsy might have clarified this problem.

Gastrointestinal disturbances are, of course, common in acute arsenical poisoning, with either organic or inorganic compounds. Recurrent, mild to moderately severe nausea, occasional vomiting, diarrhea (often alternating with constipation) are frequently observed in patients who receive inorganic arsenic, in small amounts, over a long period of time. Two of the reported patients (Cases 3 and 4) suffered from gastrointestinal distress. In the first it could have been interpreted as "psychophysiological," but for the fact that her urine arsenic excretion was ten times the normal. In the second patient, the gastrointestinal symptoms were undoubedly part of her systemic disease which included the liver damage incurred after taking the "Gay Treatment."

Ten of the remaining thirteen patients gave a history of having experienced anorexia, nausea, vomiting or diarrhea at one time or another after starting the ingestion of the "Gay" compound. Usually (seven out of ten), they noticed the gastric or intestinal distress within two to three weeks (six of seven); one patient developed nausea and anorexia after five days. The significance of these symptoms cannot be properly evaluated, since urine arsenic determinations, if done at such times, were not available to us.

The emotional and nervous disturbances noted in two of our patients (Cases 3 and 4) could be ascribed to a chronic intoxication with inorganic arsenic, but only as a suspicion. Increased irritability, insomnia, inability to concentrate, loss of memory, tremors, weakness, loss of libido, change in bowel habits have been recognized for centuries as one of the manifestations of chronic arsenical poisoning. Many of these symptoms, especially nervousness, anxiety, weakness and insomnia were present in the remaining thirteen patients. Yet, these individuals were also suffering from severe asthma of long duration. This leads often to disability, anxiety and depression, particularly in previously active males if they suffer from crippling pulmonary emphysema.[6]

None of the seventeen patients showed any peripheral blood changes suggestive of bone marrow damage. It is well known that such injury to the hematopoietic tissue can be expected, not infrequently, after the administration of massive doses of organic arsenical compounds.[9] They are unknown following the prolonged ingestion of medications containing inorganic arsenic, although potassium arsenite has a depressing effect on the leukocyte count.

Damage to the central or peripheral nervous systems was not demonstrated in any of the seventeen patients. However, in one patient (Case 3) the symptoms, namely, dizziness, weakness, nausea, vomiting were so dis-

tressing as to suggest a severe anxiety reaction. Peripheral nerve biopsies on twenty-five patients with inorganic arsenic intoxication all showed typical acute and chronic Wallerian degeneration but "nothing pathognomonic" of arsenical poisoning.[5]

Fifteen of the seventeen patients gave a positive test for arsenic when their pubic hair was examined. Seven of the seventeen patients had a urine arsenic content which exceeded the normal. It ranged from 0.06 mgms in twenty-four hours to 2 mgms (Case 1). The next highest figure, namely 1.9 mgms. occurred in a forty-six-year-old man with severe asthma and moderately severe emphysema, who had discontinued taking the "Gay Treatment" five weeks previously.

The urine arsenic content is, therefore, only an indirect measure of the degree of intoxication with inorganic arsenic. The excretion of inorganic arsenic by the kidneys becomes insignificant six weeks after the ingestion of this chemical is discontinued. At this time inorganic arsenic has been protein-fixed in the epithelial cells and, to a lesser degree, in the endothelial tissue, where the reaction to injury is now in progress.

Of the seventeen patients studied, three returned or first visited the Duke Clinic because of the failure of the "Gay Treatment," or of modifications of this regime. Ten of these seventeen patients came to the clinic, not only because of the persistence of their respiratory discomfort, but because they had also developed some manifestations of poisoning with inorganic arsenicals.

SUMMARY

1. The story of arsenic, organic and inorganic, in the treatment of chronic diseases has been discussed.

2. Seventeen patients are reported who received inorganic arsenic; usually as a component of the liquid used in the "Gay Treatment."

3. Four patients are reported in detail. Three of these had skin eruptions of varying extent due to the long-continued administration of inorganic arsenic.

4. Two patients of this group of seventeen had abnormal biochemical tests compatible with liver damage. One of these had clinical evidence of liver insufficiency. It is postulated that many more patients who have received inorganic arsenic for a prolonged time suffer some degree of liver injury.

5. The majority of these seventeen patients developed some form of gastrointestinal complaint. The symptoms appeared usually two to six weeks after the treatment was begun.

6. Only one patient out of seventeen showed laboratory and clinical evidence of renal damage. Poisoning with inorganic arsenic could not be clearly implicated. None of the other sixteen patients suffered from demonstrable renal damage.

7. The urine arsenic content indicates indirectly the degree of absorption of arsenic. Arsenic is usually not found in the urine in abnormal amounts, four to six months after the administration of this chemical. In some instances, arsenic disappears from the urine of such a patient within three weeks.

8. Inorganic arsenic can be recovered from an individual's skin, hair and nails for an indefinite time after its absorption.

Not one of the seventeen patients showed physical evidences of damage to the central or peripheral nervous system. One patient complained severely of symptoms which were interpreted as "emotional," although her twenty-four-hour urine arsenic content was 0.18 mgms.

None of the seventeen patients presented any clinical or laboratory evidence of bone marrow damage.

CONCLUSIONS

1. It must always be remembered that there is no "cure" for an inherited, constitutional affliction such as asthma. Sir William Osler stated it so well when he said "If many drugs are used for a disease, all are insufficient."[1] It is obvious that asthmatics who do not listen to the advice of their physicians will fall prey to advertised "cures."

2. It is not presumed that the "Gay Treatment" can be classed, or should be classed, under the category of "advertised cures."

3. There is no authenticated therapeutic reason why inorganic arsenic should be effective in asthma. Unfortunately, however, the treatment of diseases of unknown or undeterminable cause still remains empirical.

4. The administration of inorganic arsenic, either in the form of Fowler's solution, or as part of the "Gay Formula," is often deleterious.

5. The ingestion of inorganic arsenic produces immediate or delayed skin lesions in many individuals. The latter appear usually after three to eight years, are irreversible, and at times carcinogenic.

6. Hepatic damage occurs in patients who receive inorganic arsenic for several weeks. Liver disease of varying degree is probably more common in these individuals than we realize.

7. The seventeen patients reported here were not benefited by the administration of the "Gay Treatment," or variations of this form of treatment.

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COST OF ANTIBIOTICS

John L. Bach of Chicago, director of press relations for the American Medical Association, told a meeting of executives of Parke, Davis & Company that "for the patient, antibiotic drugs are a bargain at any price. Antibiotics have not only cancelled out many of the once fatal diseases, but they have eliminated entirely many of the bread-and-butter diseases which kept doctors so busy years ago," he said. He stressed the need for a long-range educational program by drug manufacturers to acquaint the public with the outstanding results in antibiotic development. "Five dollars worth of penicillin can eliminate the need for a $150 mastoid operation and $200 in hospital bills," he told the meeting, adding, "but does the public know this?" "When a life is at stake, the cost of any drug or drugs should be a minor consideration. Compared with early prices, antibiotic prices today are inordinately cheap. In 1944, penicillin cost $20 for an average dose of 100,000 units. Today, it is anywhere from two to eight cents for the same amount. Streptomycin came on the market at $15 a gram. Today, the same amount can be bought for fifteen cents." He urged the pharmaceutical industry to make the effort to erase the common belief that drugs are generally "too costly."

RUPTURE OF THE ESOPHAGUS

Two Instances of a Hitherto Undescribed Complication of Status Asthmaticus

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THE PHYSICIAN entrusted with the care of a patient acutely ill with bronchial asthma is responsible not alone for the alleviation of the present episode, but for the early recognition and handling of such complications as may arise. Catastrophic episodes, above all others, demand early diagnosis. Among these must be included spontaneous rupture of the esophagus, for in the untreated patient the mortality rate approaches very nearly 100 per cent, and this within twenty-four to forty-eight hours after the onset. Recently our attention has been called to two such instances in patients suffering from status asthmaticus. The absence of other reports justifies this communication.

HISTORICAL ASPECTS

The first case of spontaneous rupture of the esophagus was described by Boerhaave[6] in 1724. It concerned Baron van Wassenaer, a powerful man over fifty years of age, apparently in excellent health. He was fond of eating and, because of his prominent position and wealth, had abundant opportunity to indulge himself. After overeating he always felt a sensation of great weight in the epigastrium; this he would relieve by inducing vomiting with ipecac. On the day of the accident he had eaten an early dinner. About 10:30 that night his old disagreeable sensation returned and he drank three glasses of a hot infusion of thistle. As this was without effect he took an additional four glasses which were equally ineffective. He strove to excite vomiting by stimulating the back of his throat with his fingers. While straining violently he gave a loud cry of anguish. His servants rushed to him and he said that something had torn in the region of his stomach and the pain was so indescribable that death was surely near. Boerhaave found the Baron sitting in bed with his body bent forward almost double. He was thus supported by three servants as any other posture was intolerable. The only sign of disease was the agonizing pain. Eighteen and one half hours from the onset of his cruel suffering the Baron went into collapse and died. At autopsy twenty-four hours after death there was emphysema over the front and sides of the chest. On opening the chest, Boerhaave, who at the time knew nothing of the patient's

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last meal, detected a strong odor of roast duck. In both pleural spaces there was a large amount (104 Amsterdam ounces) of fluid corresponding in color to the reddish brown beer of which he was so fond. There was no blood. The esophagus was completely torn through transversely, the two ends retracted in opposite directions. Boerhaave is quite emphatic that there was no sign of pre-existing gastric or esophageal disease.

Isolated cases were also reported by Dryden (1787),[12] King (1842),[23] Guersent (1807),[17] Bouillaud (1823),[7] and Williams (1848)[57] over the next 125 years. The first antemortem diagnosis seems to have been reported by Joseph Meyer (1858),[32] working in Schöenlein's Clinic. His patient was a very muscular, alcoholic man, of thirty-eight, who had had episodes of dysphagia after eating solid foods since swallowing lye in childhood. These episodes gradually increased and in February, 1858, he choked on a piece of sausage. Strenuous efforts at vomiting failed to bring it up but he expelled a quantity of blood. Simultaneously severe anxiety and anguish made their appearance together with severe precordial pain. One hour later he developed subcutaneous emphysema of the right half of the face. He was given an emetic and sounded without result. He was brought to the Charité where the diagnosis was made. He died the following afternoon, fifty hours after the onset. At autopsy the esophagus was healthy up to three inches above the cardia. Here there was an ulcer which had penetrated through into the mediastinum.

Almost a century elapsed until the first operative cure was reported, but it is difficult to be certain who is entitled to this credit. Sencert (1911)[49] in France, Küttner (1918)[25] in Germany, Markowish and Svetoza (1932)[31] in Yugoslavia, and Barrett (1947)[3] in England are among the claimants. In this country the honor seems to belong to Overholt[36] of Boston (1943) who performed a left posterior mediastinotomy and bilateral pleural drainage for rupture of the esophagus. An esophageal fistula and empyema complicated the case post-operatively, but the patient survived. The briefly recorded history describes a fifty-year-old man who had been on a drinking debauch. He recovered, despite the whiskey, food and barium in his pleural cavity. Barrett[3] reported in detail the circumstances surrounding another successful operation for this condition in an early case. His patient was a forty-six-year-old woman who had suffered from asthma, but who was admitted to King's College Hospital where pelvic surgery was performed February 22, 1946. After the operation her convalescence was satisfactory until March 7, when she was about to get up. She felt sick and vomited violently. She immediately became cyanosed and dyspneic and complained of agonizing pains at the back and lower part of the thorax, as well as in the epigastrium. The correct diagnosis of ruptured esophagus was made, and, though at the time of operation she was moribund, recovery was complete.

There are at present reports of 157 patients who were victims of this

accident; fifty-five of these have been operated upon with thirty-five survivals.

CASE REPORTS

Case 1. A twenty-four-year-old white housewife,* was admitted for the final time to Charity Hospital for the treatment of status asthmaticus on November 2, 1949. She had suffered from severe bronchial asthma since the age of five years following measles. In this eighteen-year period she was hospitalized scores of times. She was never free of asthma and when she was not confined to bed she was in the Emergency Room one or more times daily for aminophylline or epinephrine. Desultory and inadequate efforts were made at allergic management, and equally poor general medical care had been offered prior to her last admission. The very chronicity of her disease engendered hostility in the resident and nursing staff. Notations by many examiners were to the effect that she was "highly emotional," a "malingerer!", an "excellent actress," "badly spoiled," "uncooperative," and the like. Throughout the years, vomiting had been a conspicuous feature of her illness.

On examination one saw a well developed and nourished, acutely ill patient propped in bed, vomiting and retching almost continuously. Respiration was labored and irregular, and was associated with classic findings of status asthmaticus. She was cyanotic and in considerable distress. There was rigidity of the upper abdomen, considered to be voluntary. Extremities were cold and moist, but the blood pressure was 150/100. The total white cell count was 18,600. Thirst was notable. The resident medical officer's opinion was: "status asthmaticus, plus psychoneurosis." She was treated with aminophylline, demerol, penicillin and oxygen. The following afternoon, after much thrashing about, she became unresponsive, deeply cyanotic, and went into severe shock. Vigorous measures were instituted and she roused. For ten minutes she was maniacal, but suddenly became very quiet. Respirations dropped to six or eight per minute and soon ceased. Artificial respiration and intracardiac epinephrine were to no avail, and she died thirty-six hours after admission.

At autopsy the relevant findings were confined to the chest. There was a left hydropneumothorax, 350 cc. of greenish watery gastric contents being found in the pleural space. There was a perforation of the lower portion of the esophagus just above the diaphragm. There was no other gross disease of the esophagus. The pathologist's summary reads as follows: "Shortly before admission, unexplained nausea and vomiting developed in a patient suffering with status asthmaticus. This became so severe that she perforated the lower portion of the esophagus with spillage of the gastric contents. The onset and termination of this was so sudden that no reactions of the pleura is seen grossly or microscopically. Apparently shortly after this she went into shock and died. Studies of the esophagus failed to reveal preexisting disease. The findings of the lungs are not typical of those seen with bronchial asthma. Other findings seen at postmortem are minor and are considered to be incidental and not related to the cause of death. In conclusion, this case may be summed up by saying that the patient died of shock due to spontaneous perforation of the esophagus."

Case 2.—L. M., a thirty-eight-year-old colored woman,† had had bronchial asthma for fourteen years, attributed to sundry foods and inhalants. Her course was reasonably smooth under allergic management though she had been hospitalized several times in status asthmaticus. Her terminal illness began March 29, 1952, while in Charity Hospital, which she had entered for study of menorrhagia.

*Charity Hospital Unit No. Ind. 42-7682.

†Charity Hospital Unit No. L.S.U. 42-216$9.

While on the Gynecology service, symptoms of bronchial asthma associated with retching and vomiting started. She was given aminophyllin intravenously with noteworthy benefit. She was discharged on April 1, though somewhat weak and dyspneic. This was premature, for it was necessary to readmit her the next day. Relevant findings on physical examination of this undernourished, emaciated, severely ill woman were those of fever (to 100 degrees), exhaustion, and status asthmaticus. She again responded well to aminophyllin by vein. The trachea was aspirated with removal of much thick mucoid sputum. A tracheotomy was done. Penicillin (400,000 units) was given every four hours; 100 milligrams of cortisone was given every two hours. The next morning (April 3) she was lying quietly in bed; the initial dehydration and exhaustion were improved. That afternoon her breathing became loud and of the Biot type; her heart rate was 180-190 per minute, and she developed nystagmus. Large amounts of thick, pink mucus were aspirated from the tracheotomy tube. She was digitalized with cedilanid because of early heart failure. Within a few hours the heart rate decreased to 120 per minute; the breathing was much improved and the nystagmus had disappeared. She vomited and retched from time to time.

On April 4 she had icy cold extremities in spite of a fever ranging between 102 and 105 degrees. At this time her asthma was no longer a problem. She was given 1000 milliliters of blood. On April 5 the blood pressure was 120/60 and the pulse rate was 92 per minute. Streptomycin was added. A crunching sound, which began with the first heart sound and lasted throughout systole, was heard and considered extracardiac by a staff physician. An electrocardiogram, as before, was suggestive of chronic pulmonary disease. Her general condition was much improved and she became afebrile. She remained afebrile until April 7 when her temperature rose to 102, and the pericardial crunch disappeared. She died at 12:30 a.m. on April 9. During the entire period in the hospital, her sensorium was clouded, and much of the time she was unresponsive to pain.

At autopsy, the main findings were myocardial infarction with mural thrombosis, and multiple infarcts of the spleen, kidneys, and brain; bronchial asthma, chronic passive congestion of the lungs and liver, and rupture of the esophagus on the anterior surface of its lower third, with mediastinitis. Section of the esophagus in the area of perforation showed complete digestion of the mucosa and submucosa, and partial digestion and necrosis of the muscularis intima. The rupture was three centimeters above the cardia and three by two centimeters in diameter. Sections of the brain cortex showed focal areas of hemorrhage throughout, some of them quite small and very little gliosis was noted around them. A few small thrombi were seen in the cerebral arteries. Section of the cerebellum showed no significant lesions.

PATHOLOGY

Although pre-existing esophagitis or stricture may predispose to rupture, it is our belief that this accident can take place in the entirely healthy esophagus.

Almost all of these tears have been in the distal portion and have been longitudinal. The cases of Boerhaave[6] and Higginson and Clagett[21] were transverse. The rent is usually situated on the postero-lateral aspect of the supracardiac portion and varies from 1 to 8 centimeters in length. It is generally unique, and involves all walls of the esophagus; at times it extends to the stomach. Occasionally the complete rupture is accompanied by smaller ones which are confined to the mucosa or submucosa. Bleicher and Girard[5] explain the site of the rupture by topographical-anatomical considerations. They point out that the esophagus is supported by resistant

tissue extending between the vena cava and the azygos vein. Only on the left is the esophagus free to dilate and to rupture. These relationships are said by Mandler[30] to have been clearly demonstrated at the Congrès de Bruxelles. Most of the ruptures which were obtained by our *in situ* experiments also took place at this locale, whereas in our experiments with isolated animal esophagi there was no preferred area of splitting. These experiments will be reported elsewhere.

Once the bursting has taken place, the gastric contents are permitted to enter the medastinum causing the characteristic severe pain, as well as a more or less rapid compression of the mediastinum. The superior mediastinal syndrome may develop but it is not classic; an increasing mediastinal emphysema which tends to exteriorize in the neck is an invariable component. The air comes from the stomach, or from aerophagia incident to subsequent attempts at vomiting or from swallowing medication or alimentation. A serosanguinous pleural effusion may follow. Under the combined effects of pressure and digestion by the gastric juice, one or both mediastinal pleurae perforate and the mediastinum empties partially, producing hydrothorax or hydropneumothorax with pulmonary collapse. There may be added an acute mediastinal displacement caused by the pneumothorax. Even if the opposite pleura is intact, sooner or later there will be a reactive pleural effusion. The changes produce the clinical symptoms. Infection and shock contribute to the extraordinary semeiologic richness.

CLINICAL PICTURE

Rupture of the esophagus spares no age group, but instances are most common in middle life and old age. There is a clear-cut preference for the male sex, as five-sixths of all cases reported occurred in men. Although there is no reason to suppose Negroes are less susceptible to the accident, the ratio is one Negro to nine white (16 to 157); this apparent discrepancy is believed to stem from the relatively large number of European reports.

The onset is usually sudden: the patient has indigestion following an excess of food or drink, and while retching or vomiting he is abruptly seized with violent pain in the epigastrium or precordium. The onset may be so fulminating that poisoning is suspected. In the case described by Raestrup[44] the police ordered an autopsy on the request of the relatives. Similarly, mineral poisoning was seriously considered as a possibility in the case of Charles.[8] At times there is a sensation of something having torn or given away.[6,8,20,38,40] Patek's[38] patient, a strong, athletic young man, after eating excessively and rapidly, felt a sensation of fullness in the epigastrium, inserted his finger in his mouth to induce vomiting and cried out in great agony: "Something has broken. I heard it and I felt it. Air! Doctor!"

The vomiting need not be related to meals to cause the rupture but may be a component of hyperemesis gradivarum,[43] or seasickness.[50] The patient of Beal[4] became nauseated and vomited while straining at stool. Cohn's[9]

patient was experiencing gastric lavage; there was about 750 cc of fluid in the stomach when, with a sudden choking motion, the tube was thrown out, and simultaneously a wave of bloody fluid came from the mouth.

Although vomiting almost invariably precedes the catastrophe, there are a number of instances recorded in which there either was no vomiting[42,52,22,24,26,] or in which pain preceded.[33,34] In Anderson's[2] third case, the patient noticed his face swell up during the meal; later he felt severe cramping abdominal pain.

The pain is located equally frequently in the epigastrium or precordium. It may be felt deep within the abdomen or chest, in the lumbar region or along the vertebral column. It is not unusual for the pain to encircle the victim at the level of the diaphragm. The pain is described as "knife-like," "stabbing," "coup de poignard" and is of such intensity as to require large quantities of opiates. There is a tendency for the pain to become more severe and to have a wider radiation as more of the irritating gastric contents are discharged into the chest. It is worsened by breathing, and respiration tends to be rapid and shallow. The discomfort is lessened by immobility; certain patients have had most relief by sitting or being held half erect, bowed forward. Thus Boerhaave[6] found the Baron van Wassenaer sitting in bed with his body bent forward almost double. Similar postures were assumed by the patients of Desjardins,[11] of Habershon,[18] and of Grammatzki.[14] Flexure of the knees on the abdomen is extremely common. Ridgeway and Duncan[45] did not turn their patient for examination "because of the agonizing pain."

The pain is worsened by swallowing, especially if brandy or the like is given. The patient of Desjardins[11] drank some coffee to attenuate the pain; the effect surpassed his expectations but in an opposite sense. Depending on the size of the esophageal rent a greater or lesser amount of the material swallowed enters the mediastinum or pleural space. If swallowing is followed by coughing, this speaks for a tear of the pleura.[19,39]

The pain may be associated with tenderness or rigidity of the abdominal wall, especially in the epigastrium or the right or left upper quadrants. The diagnosis of perforation has been frequently made in those patients who had had symptoms of peptic ulceration in the past.

Thirst may be outstanding[15,16,41,56] but is not usually commented upon. The face becomes pale, extreme anxiety and angor animi may set in; varying degrees of shock, acute collapse or even coma may supervene. More generally there is a progressive deterioration over the next few hours. Dyspnea makes its appearance in almost all instances and may be severe, progressing to orthopnea. Cyanosis is very common.

Several writers have noted alteration of the quality of the voice. In Harrison's[20] patient the tone became higher pitched and in Soupault and Couinaud's[51] patient the voice became horse. Samson[47] commented on the frequency of nasal twang which "may be of extreme importance since it often precedes the appearance of neck crepitation by several hours."

Pain may interfere with speech or may cause such groaning as to render stethoscopic examination impossible.

Particularly characteristic is the appearance of subcutaneous emphysema, ordinarily first observed in the neck just above the collar bones. It progresses slowly, usually remaining confined to the upper part of the body. It may be completely absent. Ware, Shnider and Davis[55] make the point that if emphysema is to occur it will be first noted in the mediastinum; since its presence here may antedate subcutaneous emphysema by a number of hours, these authors consider that early examination of the chest for evidence of air in the mediastinum or retrocardiac area is mandatory. In one of our patients the presence of Hamman's sign permitted the auscultatory diagnosis of mediastinal emphysema.

Chest findings are an invariable component although the type and the evolution of these varies from patient to patient. Among the commonest are dyspnea or orthopnea and cyanosis. Pleural effusion, pneumothorax, hydropneumothorax, emphysema, or reactive pleuritis and pneumonitis are often found by physical or roentgenographing examinations. Both of these latter should be repeated often because of the rapidity with which the disease progresses. Compression of the mediastinum may lead to the development of the superior mediastinal syndrome as it did in the second patient of Lindemann.[27]

Among the rarer manifestations may be mentioned those described by Roy[46] and by Lindemann.[27] In the first the patient exhibited a remarkable condition: Propped up in bed, with each expiration there projected from his mouth to a distance of three or four feet a finely divided spray of a dark brown fluid of which there seemed an endless supply. Roy explained this by analogy with a throat spray. Assuming that the cardiac orifice was closed, the esophagus as far down as the perforation could act as the vertical tube of the throat spray, and the extravasated fluid in the posterior mediastinum could be gradually aspirated into the esophagus in a finely divided state mixed with the air that almost certainly would find its way into the pleural cavity. He further assumed that when this material reached the level of the larynx, the forcible expiratory movements of the lungs could act as the bellows of the throat spray and propel the particles to a distance.

In Lindemann's case there was a loud gurgling sound as when air is blown under a fluid. Moreover on every rapid motion of the patient one could hear the characteristic bubbling; this continued for the fifteen hours he survived.

ROENTGENOLOGICAL ASPECTS

Since the radiologic findings can be either suggestive or pathognomonic of rupture of the esophagus, it is essential that at least an erect postero-anterior chest film, including the immediate subdiaphragmatic region, should be taken in all instances in which the diagnosis is suspected. Roent-

gen ray examination of the chest is the single most valuable laboratory test, and the findings are helpful in confirming the pneumothorax and pleural effusion, if present, especially when the physical examination is unsatisfactory. The lung fields should be carefully scrutinized, looking for fluid, mediastinal widening, pneumonia (unilateral or bilateral), emphysema, fluid and/or air in the mediastinum.

An early hydropneumothorax, usually caused by the irritant action of gastric contents on the mediastinal surfaces of both pleurae, will cause delayed appearance or absence of subcutaneous emphysema. The absence of mediastinal or subcutaneous emphysema points to a direct perforation into the free pleural space. Hence, hydropneumothorax indicates pleural perforation.

Pneumothorax without demonstrable fluid or with slow accumulation of fluid is so infrequently seen with rupture of the esophagus that its presence is suggestive of spontaneous pneumothorax, or spontaneous mediastinal emphysema with secondary pneumothorax.[13]

The presence of air in the tissues, usually around the base of the neck, can be detected on a roentgenogram, and is an early sign of surgical emphysema. The accumulation of air in the mediastinum courses upward, along fascial planes, under pressure; it dissects from the crura of the diaphragm into the superior mediastinum and thence into the root of the neck, and the subcutaneous tissues.[10] Air may be palpable in the neck from one[29] to twelve hours[28] after the rupture of the esophagus. It should be mentioned here that mediastinal emphysema may also be seen in rupture of the uterus or of a gastric or duodenal ulcer. Only seventy to eighty per cent of proved cases of ruptured duodenal or gastric ulcers will show subdiaphragmatic air. Therefore, in a case of mediastinal emphysema, the absence of subphrenic air rules out ruptured ulcer.[13] Subdiaphragmatic air has never been reported in spontaneous rupture of the esophagus.[42] Air behind the heart in conjunction with mediastinal emphysema is said[28] to be diagnostic of rupture of the esophagus.

The presence of a massive rapidly increasing hydropneumothorax strongly suggests spontaneous rupture of the esophagus.[35]

Demonstration of an esophageal fistula is extremely important. This is done, preferably, with lipiodol[42] and, if positive, demonstrates the site and extent of the fistula. The presence of a small amount of lipiodol in the extravasated area in the mediastinum or pleural spaces is no disadvantage and can act as a guide to the surgeon, especially in small esophageal defects. Kinsella, Morse, and Hertzog[24] feel that it is very important, diagnostically speaking, for the patient to be in the proper (upright) position for barium or lipiodol swallow. Osler Abbott[1] further states that satisfactory bedside studies can be done on comatose or moribund patients by intraesophageal instillation of a contrast medium through a Levin tube. Barium studies of the esophagus may aid in specific cases, but several films with different degrees of filling are usually necessary to detect small

lesions in the mucosal surface. Also the rapidity of barium passage in the esophagus may be such as to cause the examiner to fail to detect a small lesion, including small superficial ulceration associated with a diaphragmatic hernia or actual peptic ulceration without careful fluoroscopic study, and films *ad seriatim*.[58]

DIAGNOSIS

Knowledge of the foregoing usually permits a prompt diagnosis; indeed the diagnosis has been made over the telephone, or at a glance. When the salient features of rigidity of the upper abdomen, dyspnea and subcutaneous emphysema are lacking, and when the condition has not been precipitated by violent retching or vomiting, confusion with other entities may arise. The mistaken diagnosis of perforated peptic ulcer is commonly made, especially by surgeons. The internist more generally incorrectly ascribes the disease to acute occlusion of a coronary artery. Other states having points in common with rupture of the esophagus include acute pancreatitis, empyema of the gall bladder, spontaneous pneumothorax, acute poisoning, pulmonary embolism, rupture of the diaphragm, incarceration of a diaphragmatic hernia, renal colic, fulminating coccal infections of the kidney, acute cholecystitis, mesenteric thrombosis, splenic infarct, rupture of a subphrenic or hepatic abscess and interstitial emphysema.

The diagnosis of rupture of the esophagus is established by demonstrating the communication with the pleural cavity. A soft rubber catheter may be guided through the rent under fluoroscopic visualization or a small amount of methylene blue taken by mouth may be recovered in the pleural aspirate. The aspirate should be tested for hydrochloric acid and studied for food particles microscopically. Lipiodol may demonstrate the lesion nicely, roentgenographically. Palmer[47] visualized the defect by esophagoscopy.

PROGNOSIS

The extremely malign nature of the condition is emphasized in Figure 1 which depicts the very short survival time of untreated patients. Only 35 per cent of persons (twenty-four of seventy-one) survived twenty-four hours; eleven per cent lived to the end of the second day and none lived longer than one week.

The hazards of intellectual torpidity in diagnosis, or of delaying surgery after the diagnosis has been made, are underscored by the death of twenty-five per cent of patients within twelve hours after the accident.

By contrast, modern developments in chest surgery permit the cure of a large number of these ruptures. Such relatively simple procedures as thoracentesis or thoracotomy may prolong or even save lives; ideal results follow repair of the rent in the esophagus and cleansing of the thorax.

TREATMENT

Treatment consists essentially in immediate surgical repair of the rent via thoracotomy, satisfactory drainage of the mediastinal and pleural spaces, and supportive adjuvant therapy. Shock is not considered a contraindica-

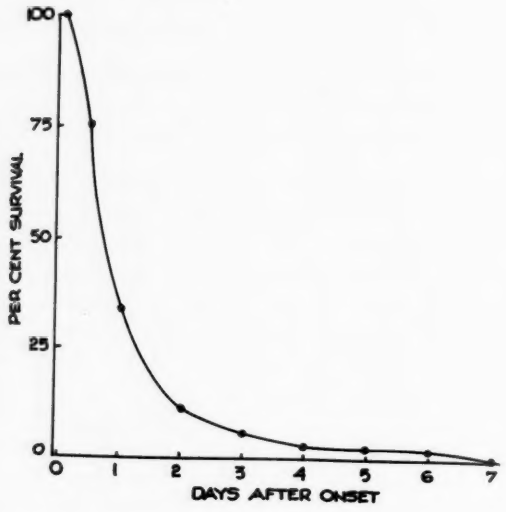

Fig. I. Survival time in seventy-one untreated rupture of the esophagus cases.

tion to surgery. Thus Scholefield's[48] second patient, a fifty-three-year-old woman, made a complete recovery though she was *in extremis* at the time of operation. The mediastinal pleura is incised throughout its entire length in order to decompress the mediastinum. This generally leads to immediate improvement. Free drainage into the pleural cavity is thus established, and this is in turn drained off by means of a tube anchored in place in the left chest, connected to a water-sealed bottle. The importance of immediate decompression of high intrapleural and mediastinal pressures is to be stressed. Samson[47] categorically states that "conservative" drainage procedures have no place in the early hours after rupture of the esophagus. He further feels that the surgical premises used in the modern treatment of wounds of a hollow viscus, i.e., prompt resuscitation exploratory operation, and closure of the defects, should be followed in spontaneous rupture of the esophagus, even though this organ is in the chest.

If a victim of this catastrophe survives for twenty-four hours, it is felt that pleural space drainage may succeed. For survivals without surgery until infection has been established, drainage procedures are helpful; but,

for drainage during the stage of contamination it is considered useless for preserving life.[47]

Ware and Strieder[56] have found that there is no difference in the survival time of control untreated animals compared with those given supportive therapy (i.e., parenteral fluids, sulfadiazine, and penicillin). The animals with the same supportive therapy but a delayed surgical repair survived longer than the first two groups. Most of those given supportive therapy and immediate benefits of surgical repair survived.

Postoperative complications mentioned by Anderson[2] include empyema, mediastinitis, and breakdown of the repair. He emphasizes adequate use of antibiotics.

Treatment consists of the following procedures:

1. Resuscitation measures, as needed.

2. Thoracentesis. This procedure alone may increase the duration of life, if immediate thoracotomy is not feasible.

3. Discontinuation of all material by mouth. A Levin tube should be inserted into the stomach, and kept under continuous suction. Parenteral alimentation.

4. Adequate antibiotic therapy, as indicated.

5. Nasal oxygen.

6. Thoracotomy, with resection of the seventh or eighth rib, then opening of the pleural cavity, and/or mediastinal cavity, establishing adequate drainage. Exposure and repair of the esophagus, by layers where possible.

7. Thorough débridement of the mediastinum, and adequate warm saline lavage of the open mediastinum and pleural cavity.

8. Re-expansion of the lung, on the affected side, as soon after surgery as possible. Bronchoscopy may be needed.

Even with the recent splendid developments in thoracic surgery, the prediction of Walker[54] that "the mortality will always be high," regrettably, is still accurate.

SUMMARY AND CONCLUSIONS

Two instances of rupture of the esophagus, believed to be the first reported as a complication of status asthmaticus, are described. The immediate cause of the catastrophe was vomiting; asthma was responsible to the extent that it caused the vomiting suffered by the patients.

Pre-existing esophagitis or stricture may predispose to rupture but the accident can take place in the entirely healthy esophagus. Almost all of these tears have been in the distal portion and have been longitudinal; two ruptures have been transverse. Rupture permits the gastric contents to enter the mediastinum; mediastinal emphysema, which may exteriorize in the neck, follows. The mediastinal pleura may rupture, producing pleural effusion, or hydropneumothorax, perhaps with pulmonary collapse. These

changes produce the clinical symptoms; additionally infection and shock contribute to the semeiology.

Most instances occur in middle life and old age; five-sixths of 157 cases were in men. The onset is sudden, typically after vomiting, with violent pain in the epigastrium or precordium. There may be a sensation of something having torn or given way. Certain postures lessen the pain; breathing, swallowing, or movement of the body worsen it. Tenderness or rigidity of the abdominal wall may be associated. Thirst may be outstanding. Several writers have noted alteration of the quality of the voice. The appearance of subcutaneous emphysema is particularly characteristic; ordinarily it is first observed in the neck. It may be completely absent. Chest findings are an invariable component but the type and evolution of these vary from patient to patient. Dyspnea and cyanosis are common. Pleural effusion, pneumothorax, hydropneumothorax, emphysema or reactive pleuritis or pneumonitis are often found by physical or roentgenographic examinations. Both of these latter should be repeated often because of the rapidity with which the disease progresses.

The condition may be readily diagnosed; common mistaken diagnoses are those of ruptured peptic ulcer or coronary occlusion. The diagnosis is established by demonstrating the communication with the pleural cavity. A soft rubber catheter may be guided through the rent with fluoroscopic assistance. Methylene blue by mouth may be aspirated, or lipiodol or barium visualized.

The accident has an extremely malign prognosis; if surgery is not performed all patients die promptly. Only 35 per cent of seventy-one patients survived twenty-four hours; 11 per cent lived to the end of the second day and none lived longer than one week. Treatment consists in immediate surgical repair via thoracotomy, drainage of the mediastinal and pleural spaces and supportive therapy. Shock is not a contraindication to surgery. Fifty-five patients have been operated on to date; of these thirty-five have survived.

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VALUE OF PERIODIC EXAMINATIONS STRESSED

Dr. H. Corwin Hinshaw of San Francisco, clinical professor of medicine, Stanford University School of Medicine, writing in the January *Bulletin* of the National Tuberculosis Association urges periodic examination in order to detect disease in its earliest phases of development so advice can be obtained on preservation of good health. He says, "People have already learned that dental examinations every six months are wise and economical. Parents have already learned to consult pediatricians for advice and care of well children. When private pediatricians cannot be had, well baby clinics are provided. Why not well papa and well mama clinics?" He stresses the fact that the actual cost of periodic health examinations by private physicians is not beyond the reach of the average working man. "Maintenance of a man costs less than maintenance of an automobile," he says. "The cost of trading the serviceable old car for a new model is greater than the cost of a major illness. Many families who spend hundreds of dollars annually on luxuries and vices are considered to be 'medically indigent.' Values and standards are distorted through ignorance and improvidence."

C-REACTIVE PROTEIN LEVELS AND ANTI-STREPTOLYSIN O TITRES IN BRONCHIAL ASTHMA

A Preliminary Report

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ATTEMPTS to differentiate and classify types of bronchial asthma associated with infection or bacterial allergy have long posed a serious problem to allergists as well as clinicians and pediatricians. The terms "intrinsic" and "extrinsic" have been used to describe types of bronchial asthma, but have recently been found to be undesirable to many allergists because no good practical method has been advanced to differentiate them.

Recently Swineford[23] has attempted to clarify this confusion by reclassifying the asthmatic syndrome. He states "most asthma is due to atopy or infection or a mixture of the two." Swineford also discusses the secondary causes of wheezing, namely reflex, physical, psychogenic and chronic lung disease, which he states become more or less unimportant when atopy and infection are controlled. Other causes of wheezing due to cardiac, asthma, bronchial obstruction and idiopathic conditions are usually not difficult to differentiate. Brown and Halpin's[9] discussion independently runs parallel to Swineford's. They divide the types of wheezing into atopic, infectious, acute and chronic, psychogenic, physical, nasogenic (or reflex), cardiac, locally obstructive and asthma due to drugs. For the purpose of this investigation, the patients were divided into three groups: atopic, infectious and mixed (atopic and infectious).

That bacterial allergy exists and may predispose, incite, and precipitate an allergic episode is well documented.[8,18,19,20] Yet with all this evidence, direct and indirect skin tests, as well as other serologic tests, often prove useless, making the diagnosis of bacterial allergy difficult.

Nose and throat cultures taken from this type of patient have revealed the marked frequency of Staphylococcus hemolyticus and hemolytic Streptococcus. Vaccines prepared from these patients have occasionally been successful in controlling their asthma; however, too often one meets with failure.

Laboratory tests in the experimental animal have shown that bacteria, their proteins, carbohydrates, etc., and their metabolites, can act as good sensitizers and evoke anaphylactic reactions.[5,6,7,19,24]

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No single method of distinguishing the various types of infectious asthma, except by history and physical findings, has yet been proposed. We have long sought for a test not too complicated, which will in some measure aid us in classifying the types of asthma with which we are confronted, in order that better therapy may be introduced promptly for the patient's benefit.

Serologic diagnostic tests have in the past proved quite useful to the clinician in the identification and subsequent treatment of infectious processes. This report is concerned with exploring the possibilities of utilizing two such serologic reactions, namely, the C-reactive Protein (C-RP) and Anti-Streptolysin O (A. S. O.) determinations, in an attempt to show the applicability or inadequacy of these tests as used for experimental differentiation of infectious processes in patients with certain asthmatic manifestations.

C-reactive Protein—A precipitin test has been developed for detecting the presence of serum C-reactive Protein which is not found in the blood of normal individuals.[1,2,12,13,14] This C-reactive Protein was first recognized by Tillett and Francis[25] in 1930, who reported the development of a precipitate when a C-polysaccharide of the pneumococcus was added to the serum of patients with acute pneumococcal pneumonia.

More recently, serial C-RP determinations were carried out by Stollerman et al,[21] who studied the usefulness and limitations of this test for the detection of rheumatic activity. This work showed evidence that there was a direct relationship between the presence of C-reactive Protein as indicative of an inflammatory process and an elevated sedimentation rate, in patients with rheumatic activity. Moreover, he observed that during cortisone therapy the sedimentation rate eventually reverted to normal and C-reactive Protein was not detectable in the blood. Whether the absence of minute quantities of C-reactive Protein in the serum would indicate that there is a process continuing below a threshold of an inflammatory stimulus required to produce a positive test is not known. However, it is of interest to note that other inflammatory manifestations may be measured in terms of C-reactive Protein precipitins.

Anti-Streptolysin O.—The anti-Streptolysin O antibody is produced as the result of antigenic stimulation by most, but not all, strains of Lancefield's group A hemolytic streptococci. The antibody appears in the serum of individuals who have been exposed to infection with these Streptococci.[10,11] Sugihara and Squier[22] attempted to determine the A.S.O. titer in respiratory allergies with indefinite results. An effort was made to determine whether there existed a pattern or sequence of elevated or depressed C-RP and A.S.O. tests in any one group of asthmatics who were diagnosed as possessing similar clinical syndrome.

It was hoped that these serologic reactions would eventually be found to aid in the differentiation of certain asthmatic infectious and non-infectious factors and at the same time be useful in therapy control in certain instances.

METHODS

Three groups of asthmatic patients, each distinguishable by certain clinical syndromes, were used in this preliminary study. Each group of patients was diagnosed by the standard criteria and classified into: Group I—infectious asthma; Group II—non-infectious (atopic) asthma; Group III—asthma with both infectious and non-infectious factors.

Blood samples were collected from one hundred and one male and female asthmatic patients ranging in age from five to seventy-one years. Thirty-five patients were diagnosed as infectious; twenty-seven as atopic, and thirty-nine as possessing a combination of infectious and atopic asthmatic syndromes. Brief but careful individual clincal records were taken regardng clinical manifestations and history of infection and treatment. Patients with a record of infection or treatment with antibiotcs, sulfonamdes, ACTH, or cortisone within two weeks prior to the time blood was drawn, were not used. Patients with a history of rheumatic fever were excluded.

C-reactive Protein precipitin tests were performed with patient's serum according to the method described by Anderson and McCarty.[3,4]* During the course of these tests, any precipitate observed, providing test serum and C-RP antiserum controls showed no precipitate, was considered a positive reaction. Anti-Streptolysin O titers were determined by a standard method as reported by Rantz and Randall[16] and Robinson.[17] Any serum giving a titer of 125 Todd units or more was arbitrarily considered positive. This is a lower titer than is usually considered as positive,[10,11,22] but was selected so as not to exclude any patient with any possibility of increased anti-Streptolysin O production.

RESULTS

The results of our studies as shown in Table I reveals the following:

In Group I (infectious) with a total of thirty-five patients, thirty gave a history of a recent upper respiratory infection, while five did not. Of the thirty with a positive history of a recent infection, seven showed the presence of C-reactive Protein precipitins, while five had positive A.S.O. titers. Of the five without a recent infection, one was positive for the C-RP test and one had a positive A.S.O. titer.

In Group II (atopic) composed of twenty-seven patients, seven gave a positive history of a recent upper respiratory infection. All were negative by the C-RP test, while two had positive A.S.O. titers. Of the twenty

*C-Reactive Protein Antiserum, Scheiffelin & Co.

TABLE I. INCIDENCE OF C-REACTIVE PROTEIN LEVELS AND ANTI-STREPTOLYSIN O TITERS IN INFECTIOUS, ATOPIC, AND MIXED-FACTOR ASTHMATIC PATIENTS

	C-Reactive Protein Intensity of ppt.					Anti-Streptolysin O Todd Units				
	Neg.	1+	2+	3+	4+	Neg.	12-100	125-250	250	QNS
Group I—Infectious†										
History of recent URI*	23	1	2	2	2	1	24	4	1	0
No history of recent URI	4	0	1	0	0	0	4	1	0	0
									Total	35
Group II—Atopic†										
History of recent URI	7	0	0	0	0	1	4	2	0	0
No history of recent URI	20	0	0	0	0	0	13	6	1	0
									Total	27
Group III—Mixed Factors†										
History of recent URI	22	5	1	1	0	1	18	7	3	0
No history of recent URI	9	1	0	0	0	0	5	4	0	1
									Total	39
Grand Total										101

†By history, physical findings, skin tests, and laboratory tests.
*URI—upper respiratory infection.

patients without a history of a recent infection, all were negative by the C-RP test, whereas seven had positive A.S.O. titers.

In Group III (mixed atopic and infectious) composed of thirty-nine patients, twenty-nine gave a positive history of a recent upper respiratory infection. Seven revealed a positive C-RP test, while ten had positive A.S.O. titers. In ten with a history of a recent infection, only one was weakly positive by the C-RP test, while four had positive A.S.O. titers.

These different groups of patients had been subjected to the usual skin tests without success and subsequent exhaustive studies involving bacterial cultures, differential counts, sedimentation rates, Weltman reaction, and leukocytic studies as described by Blatt and Nantz[5,15] without conclusive results. This led us to investigate the possibility of clarification of these results by the use of the C-RP test and A.S.O. titers. As has been shown above (Table I) in the Results, the A.S.O. titers have not been helpful, but the C-RP test has given some clues which may help us differentiate the groups previously described and discussed. When these were tabulated and carefully studied, it was noted that those patients with the so-called infectious factors showed a definite evidence of an increased C-RP in seven out of thirty cases with a history of a recent upper respiratory infection, whereas in the pure "atopic group" no increase in the C-RP was noted in seven patients with a recent upper respiratory infection, and in twenty patients with no recent upper respiratory infection. In the mixed groups (both infectious and atopic), seven out of twenty-nine with a history of a recent upper respiratory infection and one out of ten with no history of an upper respiratory infection showed an increase in C-RP titers. In all three groups the A.S.O. titers showed a general diversifica-

tion from 0 to 250 Todd units with the majority falling into the 12-100 unit group.

SUMMARY AND CONCLUSIONS

1. C-RP and A.S.O. determinations were made on one hundred and one patients with bronchial asthma.

2. The presence of C-RP in the serum of the asthmatic patient would seem to indicate the possibility of an infectious allergic process.

3. It would appear from this preliminary study that in the presence of a history of a recent upper respiratory infection with asthma, the increase in C-RP precipitate would indicate possible evidence of an allergic infectious process (factor).

4. The A.S.O. antibody seems to be so diversified that it does not lend itself as an accurate measure of infection in bronchial asthma.

5. Further plans are projected to include additional studies in the active and quiescent periods of asthmatic patients and by other methods in addition to the C-RP test and A.S.O. titers. It is hoped that this report will stimulate additional studies by other investigators which may help clarify the role of C-RP in allergic states.

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STUDY GROUP FOR PSYCHOSOMATIC ALLERGY

The first general meeting of the Study Group for Psychosomatic Allergy was held Tuesday, February 15, 1955, at 8:15 p.m. at The New York Academy of Sciences, 2 East 63rd Street, New York City. Invitations had been sent to members of The New York Allergy Society, to local members of the national allergy societies, active members of the allergy clinics, and those physicians known to have a direct interest in the clinical management of the allergic diseases. At this first meeting the general problems confronting an organization of this type were discussed. Meetings are scheduled for alternate Tuesdays for the remainder of the year. Two types of material are to be covered in the planned meetings: formal points of view in psychiatry today and discussion of case reports dealing with clinical problems of special interest to the group. It is hoped that out of these studies improved techniques of psychosomatic management of the allergic patient will be developed. Forty physicians attended the first meeting.

PNEUMOTACHOGRAPH IN A PEDIATRIC ALLERGY CLINIC
Preliminary Report

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WITHIN RECENT years, several methods have been available for the study of respiratory airflow in human beings. None of these has been entirely satisfactory. Measurement of respiratory airflow is especially difficult when one attempts to apply it to a young age group. One of these methods, the pneumograph, records chest wall movements and thus does not give adequate information about the instantaneous airflow in and out of the lungs. Because of this, we decided to use the pneumotachograph. The electrical pneumotachograph used in this study was first developed by Fleish[3] in 1925 and subsequently modified by Silverman[7] in 1944, and others.

The electrical pneumotachograph is a device for recording the instantaneous linear time rate of change in ventilation of the lungs. It consists essentially of a prime mover and a recorder. The prime mover consists of two parts in an oral-nasal mask, which contains a fine (400 mesh) Monel wire screen and a pressure manifold with ten radical ducts. In this type of respirator, dead airspace is negligible and linear recordings are possible without regard to the turbulence of the expired and inspired airflow. This airflow therefore offers a sensitive means of recording rates of change of air velocity.[2] The recorder consists of a transducer and recording galvanometer. The transducer is primarily a Wheatstone bridge in which the resistance is changed by air pressure gradient. It is hooked up to a strain gauge amplifier. The output is recorded by a galvanometer to which a heat stylus is attached. This permanently records directly on rotating paper which moves at a rate of 5 mm per second.

The pneumotachograph has been the subject of many investigations. Bretschger,[1] Silverman,[7] Kay,[4] Proctor,[5] Whittenberger[8] and many others have utilized it to gain information relative to a large number of pathologic conditions affecting the respiratory system.

The purpose of this investigation was to study, by means of the pneumotachograph, a cross section of the population of the Children's Allergy Clinic of Mount Sinai Hospital, New York City. One hundred forty tracings of 100 allergic boys and girls ranging in age from four to fourteen years were made. The major part of the work was done on asthmatic children, some asymptomatic and some with active wheezing. Similarly, tracings were done on a smaller control group of children who either had

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Fig. 1.

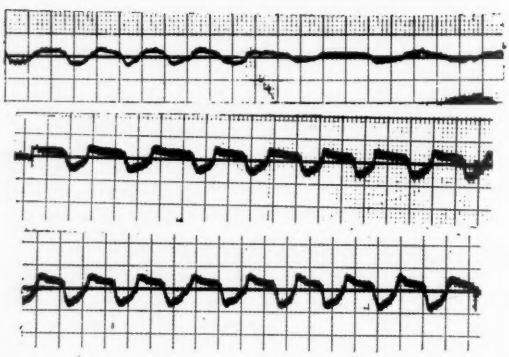

Fig. 2. *(a)* Four-year-old, male patient, shows one type of normal pattern—termed tunnel pattern. The inspiration is the mirror image of the expiration. Note the rapid breathing; *(b)* five-year-old, female (sibling of A), has had asthma four and one-half years, wheezing present, shows flattening, or plateau configuration, of expiratory phase; *(c)* same patient as in *b*, now asymptomatic. Little change is noted; *(d)* six-year-old, male, history of asthma for five years, wheezing; *(e)* same patient as in *d*, now asymptomatic.

chronic eczema or allergic rhinitis on a seasonal or perennial basis. In both groups repeated tracings were done on several children. In several cases in children who were wheezing, a reference tracing was obtained before 0.15 cc of 1:1000 epinephrine was administered, subcutaneously. After a

ten-minute interval, when the chest was clear on ascultation, a subsequent tracing was made.

The records were made with the patient seated, breathing with the mouth open and with both hands holding the mask (Fig. 1). Because there is no

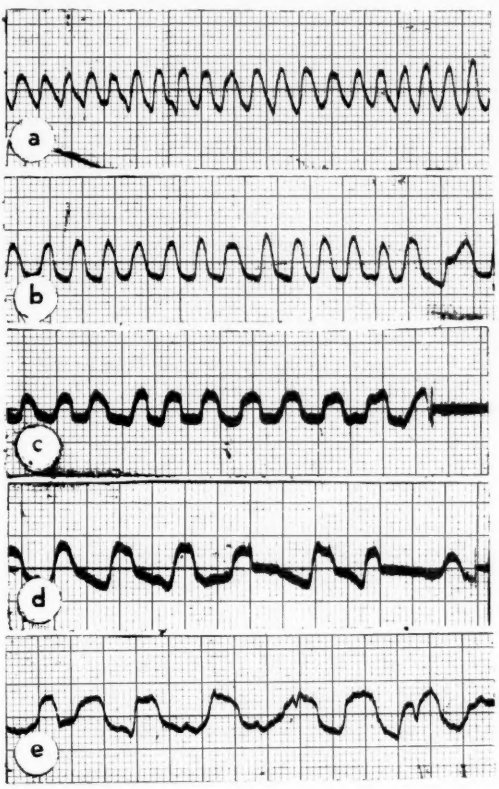

Fig. 3. *(a)* Ten-year-old, female, non-asthmatic, seasonal hayfever; *(b)* eleven-year-old, female, history of asthma, many years wheezing; *(c)* same patient as in *b*, ten minutes after 0.15 cc of Epinephrine administered subcutaneously. There is essentially no change in the configuration of the expiratory phase.

mechanical interference with breathing, we feel that unavoidable psychological reactions in children are held to minimum.

In all of these recordings the expiration is above the base line and the inspiration below (Figs. 2 and 3).

DISCUSSION

From this preliminary investigation, we see the need of more intensive study of asthmatic and normal children by means of the pneumotachograph. We believe that there is a possibility that this apparatus may be of value in the differential diagnosis of asthma in children who have repeated episodes of pulmonary infection accompanied by wheezing.

It also serves as a gauge for the prognosis of asthma as to whether there are resistance factors which may be reversible or irreversible. At this stage we feel that the prognosis of asthma in children under treatment, who have normal curves between asthmatic episodes, is more favorable than in those children where the curves remain unchanged.

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50 Central Park West

NATIONAL HEALTH COUNCIL

"Forecasting America's Health" will be the theme of the 1955 National Health Forum to be held March 23 and 24 at the Hotel Sheraton Astor in New York. This forum is sponsored annually by the forty-eight national organization members of the National Health Council. Dr. Roscoe P. Kandle, deputy commissioner of the New York City Department of Health, is chairman of the Forum Committee. The program will cover the subjects of economic trends and their relation to health planning, relationship between atomic developments and health, current government health programs, and ways in which the various groups interested in health may work together more effectively.

IDENTIFICATION OF RAGWEED ANTIGENS IN GEL DIFFUSION PRECIPITATES

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A REVIEW of the literature[13,21,32] on the chemistry of hay fever pollen shows beyond question that the active principle is a complex affair consisting of several, possibly many, more or less independent antigens. Newell[13] in his review summarizes the situation as follows: "The activity is shared probably by several substances all of which are of complex chemical natures. The molecules are smaller than those of true proteins, and one of the substances has been found to have a molecular weight of about 5000—some of the active substances contain much carbohydrate, and others resemble proteins; however, they do not fit into the accepted classification of proteins."

Since the time of Newell's review, 1941, the problem has continued to be attacked from several different angles: chemical fractionation, electrophoresis, chromatography and most recently, gel diffusion. The results of these investigations have been rather consistent in confirming the multiplicity of antigens in ragweed and other pollens and their proteose or polypeptide, and carbohydrate nature.

CHEMICAL FRACTIONATION

Stull and his associates[22,24,25] have succeeded in separating three fractions with quite different chemical and immunologic properties. Fractions one and two are water soluble, fraction three alkali soluble. Fraction one is precipitated by half saturation with ammonium sulphate, by trichloracetic acid and is inactivated by heating to 70° C at pH_4. It is precipitated by boiling, by 90 per cent alcohol or 0.5 per cent alum. It has 11.83 per cent nitrogen. Its characteristics are mainly those of protein.

Fraction two they find to be precipitated by complete saturation with ammonium sulphate and not by *trichloracetic* acid. Nor is it inactivated by heating to 70° C at pH_4. It is not precipitated by boiling, by 90 per cent alcohol nor by 0.5 per cent alum. It has only 1.75 per cent nitrogen. Its characteristics are mainly those of carbohydrate.

Fraction three is the alkali-soluble material remaining in the pollen residues after the removal of fractions one and two. Stull and has associates[24,25] describe it as soluble in weak alkali (0.01 N NaOH) and precipitated at pH_4 without heat. It is not a single entity but consists of a number of components. However, they were found to give few reactions

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with hay fever patients and failed to sensitize guinea pigs, so were regarded as unimportant by these investigators and were not studied further.

Stull and his associates[24,25] consider Fraction one to be the most important in hay fever. It was found to give more and larger skin reactions than Fraction two when used at the same protein nitrogen concentration. Occasionally, however, the reverse was found to be true, indicating that the two fractions are antigenically distinct. Moreover, they showed that each produces its specific antibody in guinea pigs and that the blocking antibody developed to one would not inhibit the reaction to the other. Fraction three was found to be antigenically different from both one and two.

Rockwell[20,21] describes a method for separating the various antigens as their hydrochlorides. One antigen is precipitated within a few hours. This antigen contains only one molecule of carbohydrate; the remaining antigens are much smaller in molecular size and each contains several molecules of carbohydrate, hence they are much more soluble and do not immediately precipitate out as the hydrochlorides. However, if allowed to stand in the cold in the presence of hydrochloric acid, the carbohydrate is converted into furfural and methylfurfural until each antigen contains only one molecule of carbohydrate, at which point it precipitates out as the hydrochloride. All of these antigens are carbohydrate flavonal-peptide complexes. Molecular weights vary from the largest which is 4496.084 to the smallest which is approximately 640. All of these fractions are immunologically and biologically active.

Fraction one Rockwell considers the major antigen, the same as Stull's Fraction one and Abramson's major unpigmented antigens, *Trifidin* and *Artefolin* (*vid. ult.*). By this method Rockwell was able to separate out from ragweed pollen five biologically active fractions.

ELECTROPHORESIS

Abramson and associates[1,2,3,4,11] have made extensive studies on pollen antigens by electrophoresis, diffusion and the ultracentrifuge. In the pollen of both tall and short ragweed, they have demonstrated the presence of a major nonpigmented, slow-moving component, which they have called *Trifidin* and *Artefolin* respectively. "There were usually also six or more minor pigmented components in both types of solution." The *Trifidin* and *Artefolin* components they found to be homogeneous in the electric field, and in the ultracentrifuge at 150,000 g they each showed a single band with the Foucault-Toepler scanning method. Data obtained from the diffusion and sedimentation constants, they found to indicate that *Trifidin* and *Artefolin* are almost identical and have molecular weights of about 5000. This, as pointed out by Rockwell, is about the same as he found for his major ragweed component. This small size, Abramson et al assert, is in accord with the ability of the pollen antigen to penetrate

human mucous membranes and to be introduced electrophorectically through the unbroken skin. Also they say: "It is conceivable that the low molecular weight of the antigen may be in part responsible for the lack of precipitin reaction."[4*]

The six or more minor and fast moving components they regard as essentially pigments or at least pigmented. They were found to be biologically active.

When most of the inactive pigments were removed from tall ragweed pollen by methanol extraction, Abramson et al[11] discovered "a new essentially unpigmented fraction" with electrophoretic mobility of 0.3μ per second at pH 7.4. "Biologic activity of the essentially pigment-free preparation is identical with the preparation containing all of the pigment." They speculate on the relationship between pigments, pigmented and unpigmented components as follows: "This new and essentially unpigmented fraction is active and conceivably would have the mobility of *Trifidin* if all the pigment could be removed—the colorless material, the major practically uncharged component, represents the biologically active molecule with groups lending the colorless molecules mobility but not biological activity. In other words, we believe that *Trifidin* is the basis of the biological activity of giant ragweed extract and that the various pigmented active molecules are in a steady state reacting with pigment groups that are readily disrupted by solvent extraction or—electrophoresis itself." A similar concept is advanced by Stevens et al.[23]

Loveless et al[12] subjected short ragweed extract to extensive dialysis and found by electrophoresis "that the shift of material through cellophane into the dialyzate had been selective involving largely those substances which were electrophoretically immobile at pH 7.5." Their experiments show at least three different specificities separable by cellophane and electrophoresis, two in the dialyzate and a third non-dialyzable component remaining in the sac. They say: "Although the extent of these gains in smaller molecular material at the expense of larger substances was not great, the shifts were suggestive of a possible breakdown taking place in the extract."

CHROMATOGRAPHY

Bernstein et al,[6] using an absorption column of alumina found that the coloring matter was strongly adsorbed in a single yellow band at the top of the column. When the latter was washed with distilled water colorless material amounting to 60 per cent of the weight of the solids in the chromatographed extract passed directly through the column. A number of fractions were collected, skin tested, and found to correspond

*It is clear from the context of this statement that the authors had in mind the precipitin reaction with human serum rather than with that of other animals in which it has long been known that precipitin against pollen can easily be produced, e.g. Parker,[18] Cromwell and Moore.[9] It is difficult to see why the smallness of the antigen molecule should cause it to discriminate between the two types of animal.

closely in activity with similar nitrogen dilutions of the original extract. "It was seen that in many instances some fractions gave reactions when the unchromatographed extract containing an equal or larger amount of nitrogen did not." Also three fractions failed to give reactions on one hay fever subject but did on another. The fractions are thus colorless and biologically different. Using paper chromatography Perlman[19] separated out two colored bands and ten uncolored. Three of the latter contained biologically active material.

Dankner and associates[10] also using paper chromatography obtained a minimum of six different active components from ragweed pollen. Five of these passed readily through a Visking membrane. Four of the diffusible components were found to be peptides of differing aminoacid composition, and one of carbohydrate material. Their six fractions these authors designated as follows in order of their translocation rates: CHO, carbohydrate, was the most rapidly moving component, followed by the five peptides, A, B, C and D, and the dialyzed residue which failed to pass through the membrane. It was demonstrated that the residue contains at least one large polypeptide or protein. Skin tests with the different fractions showed clearly that they were biologically different and that "each ragweed-sensitive subject has an individual pattern of reactivity to the smaller molecular size components: the data suggesting that most subjects are reactive to certain of the components and not to others, some are reactive to all, and a few to none." All responded to the dialyzed residue in about the same way as to the crude extract.

These authors believe it "probable that the active diffusible fractions are not the result of any solvent action on a complex but rather that they are native to ragweed extracts," although they consider the possibility that the diffusible active components may be fragments from a larger complex antigen.

GEL DIFFUSION

Becker and Munoz[5] by means of the Oudin technique[16,17] demonstrated the presence of at least five antigens in ragweed extracts. They combined rabbit antiragweed serum with agar in precipitin tubes. When this had set, it was overlaid with 5 per cent ragweed extract. As this diffused into the serum-agar mixture, five precipitation bands were formed which progressed steadily through the medium. Their distances of penetration were measured at short intervals. When these were plotted against the square root of the time they formed a straight line, thus conforming to the laws of diffusion. The authors state: "The relationship of these five antigens to the various chemical and electrophoretic fractions is not known at present."

Obviously there is a relationship of these precipitating antigens to the chemical and electrophoretic fractions, also to the equally well established

chromatographic fractions, and it is the purpose of the present investigation to discover these as far as possible.

EXPERIMENTAL

In these studies the double diffusion technique of Ouchterlony[15] was used in preference to the single diffusion technique of Oudin[16,17] employed by Becker and Munoz, since it gives more sharply defined precipitation bands and permits the direct comparison of antigenic substances which the Oudin technique does not.

Thin glass plates were coated with a layer of 2 per cent agar which was well dried, then a layer, about 1.5 mm thick, of 1 per cent agar in buffered saline (pH 7 circ.) with 1:5000 merthiolate was poured over the plates. When this had jelled, three penicillin cups were stood on the surface spaced 20 mm apart in the form of a triangle. These cups are metal cylinders open at both ends, 8 mm diam. and 9.5 mm long. Into these the reactants may be poured and allowed to diffuse into the agar. Into one of the three was put the antiserum and into the other two the pollen extracts to be compared. As the antigens and antibodies diffuse from the open ends of the cylinders and encroach upon each other, zones of equivalence become established with resultant precipitation bands. Ouchterlony has shown that each band represents at least one antigen-antibody reaction. Ordinarily the bands remain stationary but increase in intensity as more and more antigen and antibody diffuse into them from the opposing sources. Each band thus forms a barrier to the reactants that formed it, but Ouchterlony has shown that they permit the unhindered passage of all other antigens and antibodies.

The antisera used were obtained from rabbits as already described.[29] All animals responded to the pollen injections by the production of precipitin, though there were individual variations in the titers, and to some extent, the precipitation patterns of their sera.

The ragweed extracts were prepared from defatted pollen in Coca's solution without glycerin or other preservatives. Most extracts were dialyzed in cellophane sausage casings for fifteen to twenty-four hours against tap water at 4 to 7° C. This caused considerable increase in volume and the formation of a slight precipitate. The volume was reduced by evaporating before an electric fan without removing from the cellophane. The extracts were then filtered through paper, frozen and dried by sublimation.

It was found that dialysis weakened the extracts slightly but that lyophilizing had no effect on the potency or on the antigenic pattern, providing it was done without preservative. The precipitation pattern that short ragweed makes with its homologous antiserum usually has seven bands.[27] Occasionally eight may be distinguished but more often fewer can be seen at one time. A typical arrangement is that shown in Figure 3.

The bands have been lettered in the sketch by the first seven letters of the alphabet in sequence from the serum source toward the antigen source. Though this arrangement may be considered typical, it is by no means constant, varying to some extent with different antisera and different extracts. This is because the zones of equivalence between combining antigen and antibody depend upon the relative activities of the components of each, which vary from batch to batch. This makes it difficult sometimes to recognize the different bands in their various positions. Nevertheless, some have characteristics whereby they nearly always can be identified. The *a* band always forms closest to the serum source, frequently wrapped around it, and as it develops it sometimes moves right underneath the serum cup and streams out the other side (Figs. 1 and 2). This indicates that this antigen moves many times as fast as its antibody which is almost stationary. At first this band is completely amorphous without clearly defined boundaries and often with a bluish cast presenting the characteristics of the precipitates formed by carbohydrate antigens described by Oudin.[17] In a few days it condenses, becoming stringy and opalescent with a tendency to split in two or three, showing that it is not homogeneous but represents two or more closely related or structurally similar antigenic substances.

Band *b*, though not always next to *a*, can be distinguished by its prominence. It is always the most prominent so that it is justifiably called the major band. It generally forms at a considerable distance from band *a* showing that its antigen moves much slower relatively to its antibody. It is opaque, white, sharply defined and dense in appearance, entirely lacking the bluish cast of band *a*, and it shows no tendency to split, except under the stress of destructive agencies such as heat, or when formed by a heterologous but related antiserum such as that of tall ragweed.[27] This and its prominence suggest that it represents the major antigen, and that the latter is nearly homogeneous.

Next behind the *b* band are generally formed two tenuous bands. A typical arrangement is that shown (Figs. 3, *c*, *d*), but both have a tendency to be displaced in either direction, coinciding with each other, or *c* with *b* or *d* with *e*, so that these two cannot always be identified with certainty.

In the typical arrangement next comes the *e* band. It is much more prominent than *c* or *d*, but less so than *b* which it otherwise closely resembles.

(See opposite page)

Fig. 1. Dialyzed and undialyzed short ragweed extract, 200 M u/ml* compared diffiusing against their antiserum, undiluted. Their appearance after twelve days.

Fig. 2. Short ragweed extract, 300 M u/ml dialyzed, boiled ten minutes compared with the same material unheated diffusing against their antiserum undiluted. Their appearance after eight days.

*200,000 units per ml. 1 unit is 0.00001 mg N before dialysis. The latter removes most of the N but only a small part of the total activity.

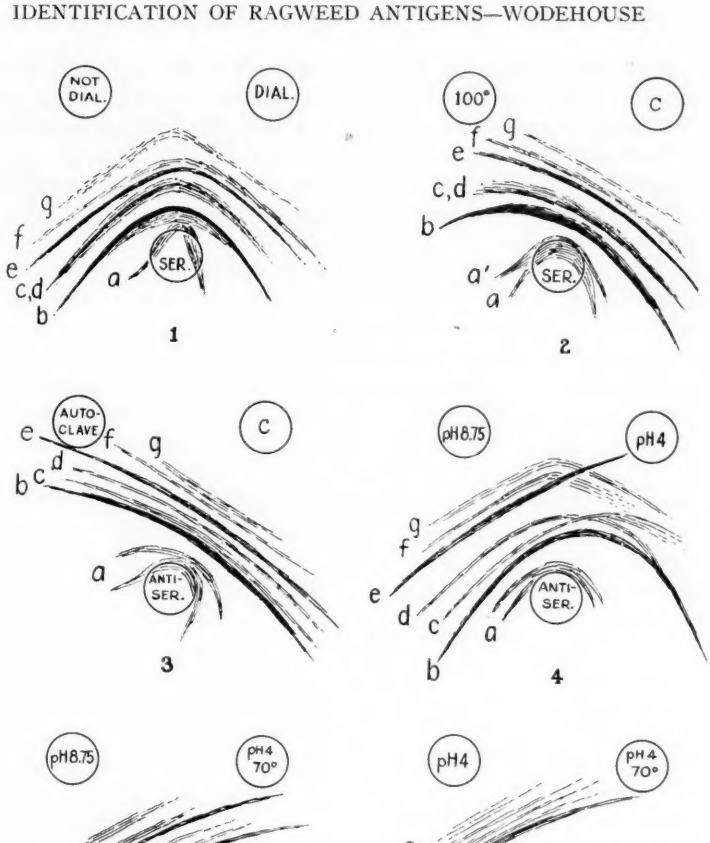

Fig. 3. Short ragweed extract, 300 M u/ml dialyzed. Fraction autoclaved at 20 lbs. 126° C. for one hour compared with unheated control diffusing against its antiserum. Appearance of their precipitation bands after eight days. Since the autoclaved fraction is nearly or quite completely inactivated, this can serve as a typical short ragweed precipitation pattern.

Fig. 4. Short ragweed 300 M u/ml dialyzed, lyophilized. Acidulated to pH$_4$ compared with unadjusted fraction diffusing against its antiserum. Appearance of precipitation bands after twelve days.

Fig. 5. As in Figure 4 but with the acidulated fraction heated momentarily to 70° C.

Fig. 6. As in Figures 4 and 5 but with the unheated acidulated fraction compared with the same heated to 70° C.

Beyond the *e* band appear two more bands (Figs. 3, *f*, *g*). They are similar in appearance to the *c* and *d* bands or even more tenuous, and their spatial arrangement is variable. Occasionally there is an eighth band which is still fainter.

Bands *b*, *e* and *a* are by far the most prominent and easy to identify, though *a* has a way of eluding detection by forming under the serum cup or so close to it that it may be obscured by a nonspecific precipitate that frequently surrounds the cup. When only three bands are present, as with very weak extracts, they are nearly always *b*, *e* and *a*, though the latter cannot always be recognized.

The basic form of this precipitation pattern, consisting of a major band together with about five to seven minor bands, one of which forms close to the serum source and generally with a bluish tint, is of common occurrence. It has been found for timothy, redtop, June grass, sweet vernal grass, orchard grass and Bermuda grass,[28] for house dust[26] and for sagebrush, Russian thistle, *Trichinella* and *Streptococcus*[31] and for *Clostridia* toxins.[7]

If it is conceded that each precipitation band represents at least one antigen-antibody reaction[14,16] the antigenic pattern of short ragweed consists of a major antigen and six or seven minor antigens, one of which, represented by the fast moving *a* band, is probably a polysaccharide haptin.[17] Similar antigenic patterns have been found by electrophoresis[2] in the pollen of timothy, June grass, orchard grass, Bermuda grass, sheep sorrel, plantain, birch and oak. It is thus seen that the antigenic structure of ragweed follows a pattern which is widespread among pollens and other antigenic substances. Serum-agar technique gives us for the first time an essentially visual representation of these antigens and a simple and certain method of examining and evaluating the effect of all kinds of forces, chemical, physical or others on their structure.

EFFECT OF DIALYSIS ON RAGWEED POLLEN EXTRACT

Dialysis was necessary in this investigation because one of its objectives was to discover the relationship between the serum agar precipitation bands and the two fractions of Stull et al which were prepared by ammonium sulphate precipitation and subsequent dialysis. Dialysis of ragweed pollen extracts also has the advantage of greatly increasing its stability under ordinary conditions, and its resistance to destructive agents. It also facilitates vacuum drying. Its one disadvantage appears to be a small loss of activity. The loss in potency of the extract through dialysis, in itself, is unimportant.[8] But, as we have seen, the different antigens have widely different molecular weights so it is reasonable to suppose that the smaller molecules would more readily escape through the dialyzing membrane than the larger, and so disturb the antigenic pattern. Indeed, as we have seen, Loveless et al have pointed out that the passage of antigenic material through the cellophane membrane is selective.

It therefore became necessary to discover what the extent of the disturbance, if any, of the antigenic pattern might be.

Short ragweed, 200 M u/ml, dialyzed for twenty-four hours against running tap water, was compared with the same material undialyzed diffusing against antishort ragweed serum (Fig. 1). Seven bands developed on each side and all interfere so as to form continuous arches. Scarcely any disturbance of the precipitation pattern can be noticed, except that the arch is slightly distorted by the bands of the dialyzed antigen forming a little closer to the serum source than from the undialyzed fraction, indicating that the dialyzed antigens are a little stronger. The arch was originally slightly displaced the other way in favor of the undialyzed material which had been shown to be slightly stronger, but owing to the more rapid deterioration of the undialyzed material than of the dialyzed the arch became displaced in favor of the latter. It is thus seen that a short dialysis of ragweed extract causes only a slight loss in activity and no observable disturbance of its precipitation pattern. This seeming contradition, as we shall see later, may be a matter of considerable theoretical importance.

EFFECT OF HEAT ON RAGWEED EXTRACT

Short ragweed extract 300 M u/ml, dialyzed twenty-four hours, was heated to 100° C for ten minutes. This was then compared with the same material unheated diffusing against antishort ragweed serum (Fig. 2). The usual seven bands are formed from the unheated control (C)—apparently bands *c* and *d* are superimposed. Bands *e*, *f* and *g* are absent from the heated side of the arch showing that their antigens were destroyed. Bands *b*, *c* and *d* are decidedly bent on the heated side showing that their antigens still retain some activity, though greatly weakened. Band *a* is split. The orientation of *a'* with its axis of symmetry directed principally toward the control shows that its antigen was largely destroyed but the other part of the *a* band makes a nearly symmetrical arch between the heated and unheated sources, showing that its antigen was not affected by heating. It is thus seen that heating under these conditions partly destroys antigens *b*, *c* and *d* and one part of antigen *a* and all of *e*, *f* and *g*.

When the same experiment was done with the same material undialyzed, the destruction of all antigens was more nearly complete, except part of *a* which remained unaffected, showing the enhanced resistance resulting from dialysis.

Heating to 60° C for thirty-two hours almost completely destroyed all bands except *a*. The *a'* part was only weakened a little, the remainder unaffected, showing that band *a* results from two substances, one more thermostable than the other but both more thermostable than any of the others under examination.

Autoclaving at 20 pounds pressure for thirty minutes was found to destroy all antigenic activity, including that of antigen *a* (Fig. 3).

EFFECT OF ACIDITY ON RAGWEED EXTRACT

An extract of short ragweed pollen which had been dialyzed and lyophilized was reconstituted and adjusted to pH_4 by adding strong HCl. A copious precipitate was formed which was removed by centrifuging. The supernatant extract was compared with the same material unadjusted, pH 8.75 (Fig. 4). The usual seven bands are formed from the unadjusted control and all except *e* are bent more or less on the acidulated side, but band *e* reaches well into the diffusion area of the acidulated fraction without any deflection indicating the total absence of its antigen from this fraction. The *b, c, d* and *f* bands are all displaced more or less toward the acidulated source showing that their antigens were weakened in varying amounts but not destroyed. Only the *a* and *g* bands remain with approximately symmetrical arches showing that their antigens were unaffected by acidulation.

In three repetitions of this experiment band *a* split, one part being weakened and the other unaffected showing partial destruction of its antigen by acidulation.

EFFECT OF HEATING TO 70° C AT pH_4

The same material that had been adjusted to pH_4 was heated momentarily to 70° C. A precipitate that formed was removed by centrifuging. The supernatant extract was then compared with the untreated control (Fig. 5) and with the unheated acidulated material (Fig. 6). In the first case it is seen that the six antigens, *b* to *g*, are absent from the acidulated heated fraction since their bands are absent on the treated side and the bands from the control extend into its diffusion area without interference. Only antigen *a* remains. Its band is split, part of it closely wrapped around the serum cup making a symmetrical arch, and part of it, marked *á*, showing a tendency to split again, in less close contact with the serum cup and making an asymmetrical arch. This shows that one part of antigen *a* is completely resistant to 70° C at pH_4 and the other partially resistant.

In the comparison of the acidulated heated fraction with the same material unheated (Fig. 6) bands which are probably *b, c, d, f* and *g* are very faint and close to the antigen cup as would be expected because they are all weakened by acidulation, and they show no interference on the heated side except a slight bending of *b* and *c*. As before the advanced part of the *a* band is wrapped closely around the serum cup forming a symmetrical arch, showing that its antigen was unaffected by either heating or acidulation, while the *á* part of this band forms only from the unheated source and extends without interference into the diffusion area of the heated material, indicating the absence of its antigen in the heated extract. It becomes evident that there is some discrepancy between these two figures. Fig. 5 shows a trace of antigen *á* but none of *b* and *c* in the

heated extract whereas Fig. 6 shows the reverse despite the fact that it is the same material in both cases. Variations of this kind are inherent to the method. In the heated extract there is far too little of the antigens *a*, *b* and *c* to form precipitates of their own, yet enough to slightly turn the ends of the precipitation bands of the unheated extracts under the most favorable conditions which may vary from experiment to experiment. We learn from this experiment that heating to 70° C at pH_4 has little or no effect on *a* antigen exclusive of *á*, but inactivates all others except traces of *á*, *b* and *c*. This calls attention to what other investigators have observed, namely the difficulty of making clean chemical separations between the antigens of pollen extracts. The difficulty lies in the nature of the antigens themselves and suggests very close chemical or structural relationships between some of them.

We are now in a position to suggest the identities of the more important antigens represented by the precipitation bands of ragweed pollen, with the antigens that have been isolated by other methods. Antigen *a*, possibly exclusive of *á*, must certainly be Stull's Fraction two. It is heat resistant and not inactivated by 70° C at pH_4 (Figs. 2, 5 and 6) and its precipitation band, including *á*, has the appearance of those given by carbohydrate haptens. It is one of Rockwell's small molecular antigens, probably the one of smallest molecular weight (MW 640). Also it must be one of Abramson's rapidly moving "pigmented" antigens. Its apparently rapid diffusion rate suggests the smallest molecular size among the antigens, but it is not pigmented nor does it shed its pigment in passing, for its precipitate forms far beyond any visible color.

It is almost certainly Dankner's fifth or most rapidly diffusing antigen, designated as CHO and shown to be primarily carbohydrate.

Antigen *b* is undoubtedly Stull's Fraction one. It produces the major band in the precipitation pattern so is most probably the major antigen. It is largely precipitated by boiling (Fig. 2) but not by acid (pH_4) without heat (Fig. 4) but is precipitated by heat and acid (70° C at pH_4). It must also correspond to Rockwell's major antigen (MW 4496.084) and Abramson's major "unpigmented" antigen, Artefolin. It probably also corresponds to Dankner's dialyzable residue only in part, because this dialyzed residue was shown by Dankner to give the same reaction pattern by skin test as the crude undialyzed extract, implying that it must contain some of all the other antigens as well as *b*.

Antigen *e* must certainly be Stull's Fraction three in part, since it is entirely removed from solution by acidulation to pH_4, but so is some of each of *c*, *d* and *f* antigens. Hence these four antigens *c*, *d*, and *f* in part and *e* in its entirety most likely constitute Stull's Fraction three, which he has shown to be a combination of minor antigens rather than a single entity.

It is scarcely possible, with the information at hand, to relate antigen *e*

with the electrophoretic fractions more than to say that it, together with *c*, *d* and *f*, represent four of the six or more "pigmented fast moving" components found in both tall and short ragweed by Abramson et al, except that neither antigen *e* nor those associated with it are pigmented and they all form in the agar beyond the range of any visible pigment which diffuses independently of the precipitation bands with an uninterrupted gradient.

Among the chromatographed fractions antigen *e* and those of its associated bands must correspond to Dankner's four diffusible peptide components. Though these are well defined by Dankner et al, they cannot be more closely related to the precipitation bands at present because of the meager data available regarding the latter. They are similar in appearance and develop very close together, frequently superimposed and their spatial arrangement is variable. Only band *e* can be recognized with certainty by its greater prominence.

It is impossible to relate the agar-diffusion precipitation bands with any of the chromatographed fractions separated by Bernstein et al[6] because these investigators failed to characterize them further than to point out that all were colorless and seven were found to be biologically active.

SUMMARY AND CONCLUSIONS

Gel-diffusion patterns of short ragweed extract show that there are at least eight antigens present. One of these is major, the others minor in varying degree. The most rapidly diffusing of these, the one which forms its precipitate closest to the serum source, is apparently largely carbohydrate. In these respects the pattern corresponds to those of most other pollens and at least some other allergens. The results of gel-diffusion are in harmony with the findings by chemical fractionation, electrophoresis and chromatography.

Both the antigens and their homologous antibodies are separate entities, and the antigens are not determinant groups permanently attached to a single large molecule, because they form separate precipitation bands by both the double diffusion technique of Ouchterlony and single diffusion technique of Oudin.

Some of the antigens represented by these precipitation bands have been identified with a fair degree of certainty with the antigens revealed by three other techniques.

All except one, which is, at least in part, the major antigen, are dialyzable through cellophane membranes. The diffusible antigens constitute a relatively small proportion of the total antigenicity.[4,10,12] Their origin is uncertain. However, the fact that dialyzable antigenic material may be removed from the extract without noticeably altering the antigenicity of the undialyzed fraction,[10] and the fact that dialysis of the extract does not materially alter its precipitation pattern, lends support

to the suggestion of Dankner et al and of Loveless et al that the dialyzable antigens are fragments from the undialyzable fraction. The lack of disturbance of the precipitation pattern by dialysis also suggests that as they are removed from the sac they are renewed by further fragmentation resulting in a diminishing activity of the sac contents but little or no disturbance in its antigenic pattern.

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Preliminary Program

GRADUATE INSTRUCTIONAL COURSE IN ALLERGY

April 25-27, 1955

and

ELEVENTH ANNUAL CONGRESS

THE AMERICAN COLLEGE OF ALLERGISTS, INC.

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COMMITTEE AND BOARD MEETINGS

Sunday April 24		
Board of Directors Meeting	8:00 a.m.	Walnut Room
Joint Meeting — Certification Committee and Board of Regents	9:00 a.m.	Walnut Room
Board of Regents Meeting	10:00 a.m.	Walnut Room
Wednesday, April 27		
Standardization (including sub-committees for Certification of Allergenic Extracts and Standardization of Aerosol Therapy)	9:00 a.m.	Parlor C
Pollen	9:00 a.m.	Parlor A
Bylaws	10:00 a.m.	Parlor A
Editorial Board	11:00 a.m.	Parlor C
New & Unused Therapeutics	2:00 p.m.	Parlor A
Public Education	3:00 p.m.	Parlor A
Friday, April 29		
Psychosomatic Allergy	8:00 p.m.	Walnut Room
Dermatologic Allergy	8:00 p.m.	Constitution Room
Saturday, April 30		
New Board of Regents	8:30 a.m.	Walnut Room
Ophthalmology & Otorhinology	10:50 a.m.	Parlor C
Pediatric Allergy	11:00 a.m.	Constitution Room

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Eleventh Annual Graduate Instructional Course in Allergy

(Preliminary Program—subject to minor changes)

MONDAY, APRIL 25, 1955

Morning Session—Grand Ballroom

FUNDAMENTALS OF ALLERGY

Chairman: LAWRENCE J. HALPIN, M.D., Cedar Rapids, Iowa
Assisting: DAVID R. THOMAS, JR., M.D., Augusta, Georgia

8:00—Registration—Ballroom Foyer

9:00—The Introduction to the Diagnosis of Allergic Conditions
M. MURRAY PESHKIN, M.D., Consulting Allergist, The Mount Sinai Hospital, New York, New York

9:30—Immunology as Applied to Allergy
JOHN H. VAUGHAN, M.D.,* Department of Medicine, Medical College of Virginia, Richmond, Virginia

10:00—Etiology of Allergy
JONATHAN FORMAN, M.D., Editor, Ohio State Medical Journal; Lecturer in Allergy and Professor of Medical History, Ohio State University College of Medicine, Columbus, Ohio

10:40—Allergic Skin Reactions and the Theory of Histamine
HAROLD A. ABRAMSON, M.D., Associate Physician and Chief, Allergy Clinic, The Mount Sinai Hospital, New York, New York

11:10—Classification of Hypersensitive States
ORVAL R. WITHERS, M.D., Kansas City, Missouri, Head of Allergy Clinic, Associate Clinical Professor of Medicine, University of Kansas School of Medicine, Kansas City, Kansas

11:40—Pathology of Allergy
ISRAEL DAVIDSOHN, M.D.,* Professor of Pathology, Chest Department, Chicago Medical School; Director of Research, Mount Sinai Research Foundation; Director, Department of Pathology, Mount Sinai Hospital, Chicago, Illinois

12:10—Diagnostic Methods—Evaluation of Skin Tests
MERLE W. MOORE, M.D., Associate Clinical Professor of Medicine, Head of Division of Allergy, University of Oregon Medical School, Portland, Oregon

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*By invitation

LUNCHEON—Constitution Room

12:30-2:00 p.m.

Chairman: JOHN MITCHELL, M.D., Columbus, Ohio

Assisting: WALTER E. OWEN, M.D., Peoria, Illinois

Guest Speaker: SMITH FREEMAN, M.D.,* Professor of Biochemistry and Chairman of Department of Biochemistry, Northwestern University Medical School, Chicago, Illinois

Steroids, Stress and Adaptation in Allergy

MONDAY, APRIL 25, 1955

Afternoon Session—Grand Ballroom

RESPIRATORY ALLERGY

Chairman: THERON G. RANDOLPH, M.D., Evanston, Illinois

Assisting: VERNON WIKSTEN, M.D., Topeka, Kansas

Nasal Allergy

2:00—The Diagnosis of Seasonal Hay Fever
JAMES E. STROH, M.D., Clinical Assistant Professor of Medicine, University of Washington, Seattle, Washington

2:25—The Diagnosis of Perennial Allergic Rhinitis
L. DELL HENRY, M.D., Lecturer in Speech Pathology, Department of Speech, Staff Physician, Speech Clinic, University of Michigan, Ann Arbor, Michigan

2:50—The Specific Treatment of Acute and Chronic Hay Fever
HARRY L. ROGERS, M.D., Chief of Allergy Clinic, Outpatient Department, Cooper Hospital, Camden, New Jersey; Assistant Professor of Clinical Medicine, Jefferson Medical College, Philadelphia; Chief of Allergy Clinic, Jefferson Hospital, Philadelphia, Pennsylvania

3:15—The Symptomatic Treatment of Perennial Nasal Allergy
MARK H. MOTHERSILL, M.D., Outpatient Allergy Clinic, General Hospital, Indianapolis, Indiana

*By invitation

Bronchial Asthma

3:50—Diagnostic Procedures

JAMES A. MANSMANN, M.D., Assistant Professor of Medicine, University of Pittsburgh Medical School, Pittsburgh, Pennsylvania

4:15—Differential Diagnosis from Cardiovascular Conditions

CLARENCE BERNSTEIN, M.D., Orlando, Florida; Regional Consultant, National Jewish Home for Asthmatic Children, Denver, Colorado; and S. D. KLOTZ, M.D., Orlando, Florida, Consultant in Medicine, Patrick Air Force Hospital, Cocoa, Florida

4:40—Differential Diagnosis from Pulmonary Conditions

MEYER R. LICHTENSTEIN, M.D.,* Medical Director, Municipal Tuberculosis Sanatorium, Chicago; Clinical Assistant Professor of Medicine (Allergy), University of Illinois School of Medicine, Chicago, Illinois

5:05—Pulmonary Function Tests: Their Significance and Practical Application

GORDON L. SNIDER, M.D.,* Assistant Director, Chest Department, Michael Reese Hospital, Chicago, Illinois

(Each paper will be followed by a 5-minute Question and Answer period. Written questions may also be submitted to Chairmen or Assistants at any time during Course to be answered at Allergy Clinical Conference on Wednesday evening.)

MONDAY, APRIL 25, 1955

Evening Panel—Grand Ballroom—8:00-10:00 p.m.

PHYSIOLOGIC METHODS IN THE THERAPY OF CHRONIC BRONCHIAL ASTHMA, PULMONARY EMPHYSEMA, AND ALLIED DISORDERS

(Panel will discuss the various pulmonary pressure machines and inhalant therapy.)

Chairman: MAURICE S. SEGAL, M.D., Boston, Massachusetts

Assisting: ALLAN HURST, M.D., Denver, Colorado

Panel Members:

LOWELL HENDERSON, M.D., Section of Medicine, Mayo Clinic, Rochester, Minnesota

EDWARD J. LEVINE, M.D.,* Assistant Professor of Clinical Medicine, Chicago Medical School; Attending Physician, Cook County Hospital, Chicago, Illinois

GORDON L. SNIDER, M.D.,* Assistant Director, Chest Department, Michael Reese Hospital, Chicago, Illinois

LEON UNGER, M.D., Assistant Professor, Northwestern University School of Medicine; Attending Physician, Cook County Hospital, Chicago, Illinois

*By invitation

TUESDAY, APRIL 26, 1955

Morning Session—Grand Ballroom

RESPIRATORY ALLERGY

Chairman: L. Everett Seyler, M.D., Dayton, Ohio

Assisting: Fred O. Kuehl, M.D., Green Bay, Wisconsin

9:00—Treatment of Bronchial Asthma in Adults
W. H. Browning, M.D., Shreveport, Louisiana

9:25—Practical Management of Bronchial Asthma in Childhood
Morris A. Kaplan, M.D., Assistant Professor of Medicine, Chicago Medical School, Director of Allergy Research Unit, Chicago Medical School and Mount Sinai Research Foundation, Chicago, Illinois

9:50—The Management of Status Asthmaticus (Including Complications)
Giles A. Koelsche, M.D., Consultant, Division of Medicine, Mayo Clinic, Rochester, Minnesota

10:15—Differential Diagnosis of Wheezing—Bronchoscopic Clinic (movie)
Paul H. Holinger, M.D.,* Professor of Broncho-esophagology, Department of Otolaryngology, University of Illinois College of Medicine; Senior Attendant in Broncho-esophagology, St. Luke's Hospital, and Attendant in Broncho-esophagology, Children's Memorial Hospital Clinic, Chicago, Illinois

10:50—Cor Pulmonale in Bronchial Asthma and Emphysema
Cecil M. Kohn, M.D., Chief of Allergy Department, Kansas City General Hospital, Kansas City, Missouri

11:15—How to Examine For and Evaluate Otorhinolaryngologic Findings
Sam H. Sanders, M.D., Associate Professor of Otolaryngology, University of Tennessee Medical School, Memphis, Tennessee

11:40—Emotional Problems in Childhood Allergy
Hyman Miller, M.D., Beverly Hills, California; Associate Clinical Professor of Medicine, University of California at Los Angeles Medical School

12:05—Roentgenographic Evaluation of Pulmonary Emphysema
J. B. Rushing, M.D.,* Houston, Texas

(Each paper will be followed by a 5-minute Question and Answer period. Written questions may also be submitted to Chairmen or Assistants at any time during Course to be answered at Allergy Clinical Conference on Wednesday evening.)

LUNCHEON—Constitution Room

12:30-2:00 p.m.

Chairman: Leon Unger, M.D., Chicago, Illinois

Assisting: Walker L. Rucks, M.D., Memphis, Tennessee

Guest Speaker: Andrew L. Banyai, M.D.,* Past President, American College of Chest Physicians; Associate Clinical Professor of Medicine, Marquette University School of Medicine, Milwaukee, Wisconsin

Treatment of Emphysema Secondary to Bronchial Asthma

*By invitation

TUESDAY, APRIL 26, 1955

Afternoon Session—Grand Ballroom

DERMATOLOGIC ALLERGY

Chairman: MAYER A. GREEN, M.D., Pittsburgh, Pennsylvania

Assisting: MAURICE C. BARNES, M.D., Waco, Texas

2:00—Diagnosis of Childhood Eczema

JAMES R. WEBSTER, M.D., Professor of Dermatology, Northwestern University Medical School, Chicago, Illinois

2:25—Electrolytes in the Treatment of Eczema in Early Childhood

IRVIN H. MOORE, M.D., Minneapolis, Minnesota

2:50—Treatment of Infantile Eczema

DAVID M. COHEN, M.D.,* Professor of Dermatology, University of Chicago Medical School, Chicago, Illinois

3:15—Common Causes of Contact Dermatitis

SAMUEL J. ZAKON, M.D.,* Assistant Professor of Dermatology, Northwestern University School of Medicine, Chicago, Illinois

3:50—Modern Therapy of Contact Dermatitis

ROBERT G. CARNEY, M.D.,* Professor of Dermatology and Syphilology, University of Iowa; Consultant, U. S. Veterans Hospital, Iowa City, Iowa

4:15—Perianal and General Pruritus

GEORGE A. WALDBOTT, M.D., Instructor, Wayne University College of Medicine, Detroit, Michigan

4:40—Some Psychosomatic Aspects of Food Allergy

WILLIAM KAUFMAN, M.D., Joint Editor-in-Chief, International Archives of Allergy and Applied Immunology; Contributing Editor, Quarterly Review of Allergy and Applied Immunology; President, Academy of Psychosomatic Medicine, Bridgeport, Connecticut

5:05—Causes and Management of Chronic Urticaria and Angioedema

MILTON J. STEINHARDT, M.D., Instructor, Wayne University College of Medicine; Allergy Clinics and Staffs of Receiving, Grace, and Sinai Hospitals, Detroit, Michigan

(Each paper will be followed by a 5-minute Question and Answer period. Written questions may also be submitted to Chairmen or Assistants at any time during Course to be answered at Allergy Clinical Conference on Wednesday evening.)

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*By invitation

TUESDAY, APRIL 26, 1955

Evening Panel—Grand Ballroom—8:00-10:00 p.m.

OFFICE MANAGEMENT

Chairman: HOMER E. PRINCE, M.D., Houston, Texas

Assisting: CARL D. MARSH, M.D., Memphis, Tennessee

Panel Members:

Public Relations—MR. LEO BROWN, Director of Public Relations, American Medical Association, Chicago, Illinois

Group Practice—JOHN GILLASPIE, M.D., Mayor of the City of Boulder, and Director of Boulder Clinic, Boulder, Colorado

Patient and Physician Relationship—LEON UNGER, M.D., Assistant Professor, Northwestern University School of Medicine; Attending Physician, Cook County Hospital, Chicago, Illinois

Personnel—MR. NORMAN D. BAILEY, Executive Director, Grant Hospital, Chicago; Professor of Personnel Administration, Northwestern University, Chicago, Illinois

Business Procedures—MR. MILLARD K. MILLS, General Manager, "Professional Management," Waterloo, Iowa

OR

Workshop—Parlor C—8:00-10:00 p.m.

AMERICAN MEDICAL WRITERS' ASSOCIATION

Chairman: JONATHAN FORMAN, M.D., Columbus, Ohio

Assisting: LEE VAN ANTWERP, M.D.,* President, American Medical Writers' Association, Chicago, Illinois

ETHAN ALLAN BROWN, M.D., Boston Massachusetts; Editor, *Annals of Allergy*

*By invitation

WEDNESDAY, APRIL 27, 1955

Morning Session—Grand Ballroom

MISCELLANEOUS ALLERGY

Chairman: VINCENT J. DERBES, M.D., New Orleans, Louisiana

Assisting: DELBERT J. PARSONS, M.D., Springfield, Ohio

9:00—Botany of Allergy

ROGER P. WODEHOUSE, Ph.D., Associate Director of Research in Allergy, Lederle Laboratories, Pearl River, New York

9:25—Allergy of the Alimentary Tract

PHILIP M. GOTTLIEB, M.D., Instructor in Medicine, University of Pennsylvania; Chief of Allergy, Kensington Hospital; Associate Allergist, Jewish Hospital; Allergist, Sidney Hillman Medical Center, Philadelphia, Pennsylvania

9:50—Physical Allergy

R. DALE DICKSON, M.D., Topeka, Kansas

10:15—Headache and Allergy

ALBERT H. UNGER, M.D., William Beaumont Army Hospital, El Paso, Texas; Instructor in Medicine, Northwestern University Medical School (on leave) and Attending Staff, Columbus Hospital, Chicago, Illinois (on leave).

10:50—Allergy to Drugs

J. WARRICK THOMAS, M.D., Assistant Professor, Clinical Medicine, Medical College of Virginia, Richmond, Virginia

11:15—Allergy to Insects

RICHARD L. ETTER, M.D., Instructor in Clinical Medicine, Baylor University College of Medicine; Associate in Allergy, Hermann Hospital, Houston, Texas

11:40—Allergy to Foods

RALPH HALE, M.D., Kansas City, Missouri; Instructor in Medicine, University of Kansas School of Medicine, Kansas City, Kansas

12:05—Inhalant Allergy in Industry

STEPHEN D. LOCKEY, M.D., Allergist, Lancaster General Hospital, Lancaster, Pennsylvania

(Each paper will be followed by a 5-minute Question and Answer period. Written questions may also be submitted to Chairmen or Assistants at any time during Course to be answered at Allergy Clinical Conference on Wednesday evening.)

LUNCHEON—Cotillion Room

12:30-2:00 p.m.

Chairman: HARRY S. BERNTON, M.D., Washington, D. C.
Assisting: RALPH HALE, M.D., Kansas City, Mo.

Guest Speaker: FRED W. WITTICH, M.D., Minneapolis, Minnesota; Secretary-Treasurer, American College of Allergists; President, International Association of Allergology

Respiratory Allergies and Their Modifications in Patients Over Forty-five Years of Age

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*By invitation

WEDNESDAY, APRIL 27, 1955

Afternoon Session—Grand Ballroom

NEWER CONSIDERATIONS OF THE ALLERGIES

Chairman: LESTER BARTLETT, M.D., Pittsburgh, Pennsylvania

Assisting: JOHNNY BLUE, M.D., Oklahoma City, Oklahoma

2:00—Mold Allergy

NATHAN SCHAFFER, M.D., Chief of Allergy, Orange Memorial Hospital, East Orange, New Jersey

2:25—Steroid and Hormone Therapy in Asthma

S. H. JAROS, M.D., Chief, Allergy Clinic, Division of Internal Medicine, Grasslands Hospital, Valhalla, New York

2:50—The Role of Infection in Allergy

MORRIS SCHERAGO, D.V.M., Professor and Head of Department of Bacteriology, University of Kentucky, Lexington, Kentucky

3:15—Pharmacology in Allergies

M. COLEMAN HARRIS, M.D., Chief of Allergy, San Francisco Polyclinic and Postgraduate College, San Francisco, California

3:50—Evaluation of Methodology of Psychotherapy in Allergy

HAROLD A. ABRAMSON, M.D., Associate Physician and Chief, Allergy Clinic, The Mount Sinai Hospital, New York, New York

4:15—Management of the Pre-allergic Child

NORMAN W. CLEIN, M.D., Children's Clinic; Clinical Assistant Professor of Pediatrics, University of Washington School of Medicine, Seattle, Washington

4:40—Smoking and Respiratory Allergy

HENRY D. OGDEN, M.D., Assistant Professor, Department of Medicine, Louisiana State University School of Medicine, New Orleans, Louisiana

5:05—What is an Allergist?

ETHAN ALLAN BROWN, M.D., Lecturer in Allergy, Tufts College Medical School; Physician-in-Chief, Allergy Section, Boston Dispensary Unit, New England Medical Center, Boston, Massachusetts

(Each paper will be followed by a 5-minute Question and Answer period. Written questions may also be submitted to Chairmen or Assistants at any time during Course to be answered at Allergy Clinical Conference on Wednesday evening.)

WEDNESDAY, APRIL 27, 1955

Evening Panel—Grand Ballroom—8:00-10:00 p.m.

ALLERGY CLINICAL CONFERENCE

Chairman: GEORGE ROCKWELL, M.D., Weslaco, Texas
Assisting: WILLIAM C. SERVICE, M.D., Colorado Springs, Colorado

Panel Members:
ETHAN ALLAN BROWN, M.D., Boston, Massachusetts
LAWRENCE J. HALPIN, M.D., Cedar Rapids, Iowa
M. MURRAY PESHKIN, M.D., New York, New York
SAM H. SANDERS, M.D., Memphis, Tennessee
MAURICE S. SEGAL, M.D., Boston, Mass.
ALBERT V. STOESSER, M.D., Minneapolis, Minnesota
JAMES R. WEBSTER, M.D., Chicago, Illinois
(Oral and written questions will be answered at this session)

OR

WEDNESDAY, APRIL 27, 1955

Parlor C—8:00-10:00 p.m.

ASSOCIATION OF ALLERGISTS FOR MYCOLOGICAL INVESTIGATION, INC.

All interested allergists are invited to the scientific meeting. Members of the Association will remain for the annual business meeting.

Chairman: HOMER E. PRINCE, M.D., Houston, Texas

Assisting: SIM HULSEY, M.D., Fort Worth, Texas

8:00—Sensitization to Airborne Bacteria—A Clinical Report
L. O. DUTTON, M.D., El Paso, Texas

8:15—Atmospheric Molds, Actinomycetes, Yeasts, and Bacteria: A Seasonal Study Including a Dust Storm
MARIE B. MORROW, Ph.D., and GEORGE H. MEYER, M.A.,* Austin, Texas

8:30—Discussion on the first two papers.

8:40—Comparative Skin Tests of Antigens Prepared by the No. 33 Technique from a Non-Sporulating and from a Sporulating Alternaria
MORRIS A. KAPLAN, M.D., Chicago, Illinois; HOMER E. PRINCE, M.D., Houston, Texas; and MARIE B. MORROW, Ph.D., Austin, Texas

9:00—Regional Airborne Molds: Further Reports
MARIE B. MORROW, Ph.D., Austin, Texas

9:20—Comparative Skin Tests of House Dust Extracts Prepared by the No. 33 Technique with Dusts Prepared by Other Processes
WILLIAM H. BROWNING, M.D., Shreveport, Louisiana; Chairman, Subcommittee for the Study of Dust Extracts Prepared by Various Techniques

9:40—Further Observations on Tests and Treatment with Pathogenic Fungi, Trichophytin and Candida (Monilia) Albicans, Prepared by Technique No. 33. A Collaborative Study
BOEN SWINNY, M.D., San Antonio, Texas; Chairman, Subcommittee on the Study of Extracts of Pathogenic Fungi

*By invitation

MONDAY THROUGH FRIDAY—APRIL 25-29, 1955

(Parlor D)

9:00 a.m. to 5:00 p.m.

OFFICE AND LABORATORY PROCEDURES

Under the direction of: Morris Kaplan, M.D., Chicago, Illinois
Assisted by: Leon Unger, M.D., Chicago, Illinois
Stephen D. Lockey, M.D., Lancaster, Pennsylvania
French K. Hansel, M.D., St. Louis, Missouri
and their associates.

1. **Management of the allergic patient: history taking; demonstration of history and testing forms in common use; application of additional aids in diagnosis and investigative procedures.**
2. **Lectures and demonstrations on the extracting and preparation of house dust, polyvalent epidermal, pollen, mold and food extracts.**
3. **Preparation and dilution of testing materials.**
4. **Demonstrations of various methods of testing: dermal, endermal, patch, intraocular, insufflation, et cetera.**
5. **Preparation of polyvalent epidermal, pollen, and mold treatment sets.**
6. **Preparation of autogenous vaccines.**
7. **Miscellaneous laboratory procedures; demonstrations of various simple laboratory procedures, pulmonary function tests, cytologic examination and application, et cetera.**
8. **Opportunity to obtain authoritative advice concerning any laboratory problem or procedure applicable to allergy practice.**

Fee for the Instructional Course is $50, which DOES NOT include the three luncheons.

This Course has been approved for informal credit by the Commission on Education of the American Academy of General Practice.

TECHNICAL EXHIBITS

During the mid-morning and mid-afternoon of each of the three days of the Scientific Program, it is imperative that a half hour be allotted for visiting the exhibits. The chairman of each section is instructed to call a recess at this time, and participants have received printed instructions from the Over-all Chairman to prepare their papers so as to adhere to the time limits.

We are obligated by contract to extend this courtesy to our exhibitors. If it were not for them it would be impossible to finance annually a successful program on an extensive scale. You will find this year's Technical Exhibits extraordinary, and worthy of your time. The representatives will be pleased to receive any suggestions or comments you may make. Many of these exhibitors are advertisers in the "ANNALS OF ALLERGY" and/or Sustaining Members of the College.

Your co-operation in showing our appreciation to the Technical Exhibitors is earnestly requested.

Eleventh Annual Congress

(Preliminary Program—subject to minor changes)

WEDNESDAY, APRIL 27, 1955

2:00—Registration—Ballroom Foyer

8:00—Scientific Program of The American Association for Mycological Investigation. **(See page 65)**

THURSDAY, APRIL 28, 1955

Morning Session—Constitution Room

GENERAL SESSION

Chairman: MERLE W. MOORE, M.D., Portland, Oregon

Assisting: G. F. HEIBER, M.D., St. Petersburg, Florida

9:00—Welcome

MAX SAMTER, M.D., President, Chicago Allergy Society

9:05—Response

HOMER E. PRINCE, M.D., President, American College of Allergists

9:10—The Technique of Respiratory and Physical Exercise in the Treatment of Bronchial Asthma

BERNARD T. FEIN, M.D., and EUGENIA P. COX, B.A.,* San Antonio, Texas

Discussion: LEON UNGER, M.D., Chicago, Illinois

9:30—The Use of Gel Diffusion Techniques in the Study of Allergens

ROGER P. WODEHOUSE, PH.D., Pearl River, New York

Discussion: MORRIS A. KAPLAN, M.D., Chicago Illinois

9:50—Allergic Factors in an Unusual Case of Pemphigus Treated by Means of Cortisone and Allergic Therapy

BERNARD M. ZUSSMAN, M.D., Memphis, Tennessee

10:00—The Management of the Allergic Patient During Pregnancy

A. L. MAIETTA, M.D., Boston, Massachusetts

Discussion: ETHAN ALLAN BROWN, M.D., Boston, Massachusetts

10:20—RECESS TO VISIT EXHIBITS

Chairman: CECIL M. KOHN, M.D., Kansas City, Missouri

Assisting: S. H. CARSLEY, M.D., Cranford, New Jersey

10:50—Psychogenic Eczema in Childhood

HAROLD A. ABRAMSON, M.D., New York, New York

Discussion: M. MURRAY PESHKIN, M.D., New York, New York

11:10—Speed of Action of Intravenous Hydrocortisone in Asthma

WILLIAM GRATER, M.D., Dallas, Texas

Discussion: BERNARD T. FEIN, M.D., San Antonio, Texas

11:30—Educational Opportunities in Allergy

JOHN SHELDON, M.D.,* Ann Arbor, Michigan; President, American Academy of Allergy

*By invitation

12:30—LUNCHEON—Grand Ballroom

Chairman: J. Warrick Thomas, M.D., Richmond, Virginia

Guest Speaker: Harry Alexander, M.D., Emeritus Professor of Clinical Medicine, Washington University Medical School; Former Editor, *Journal of Allergy*, St. Louis, Missouri

Death from Asthma

THURSDAY, APRIL 28, 1955

Afternoon Session—Constitution Room

Chairman: Harry L. Rogers, M.D., Philadelphia, Pennsylvania

Assisting: Lowell Henderson, M.D., Rochester, Minnesota

2:00—The Value of Bronchoscopy in Asthma

Joseph D. Howell, M.D., Indianapolis, Indiana
Discussion: Herbert S. Dieckman, M.D., Evansville, Indiana

2:20—Antihistaminics for Allergic and Pyrogenic Transfusion Reactions

Rudolf E. Wilhelm, M.D., Dearborn, Michigan; Helen M. Nutting, A.B.,* Grosse Pointe, Michigan; Elmer R. Jennings, M.D.,* Detroit, Michigan; and Osborne A. Brines, M.D.,* Detroit, Michigan
Discussion: S. William Simon, M.D., Dayton, Ohio

2:40—Osteoporosis and Compression Fractures from Prolonged Cortisone and Corticotropin Therapy

William S. Eisenstadt, M.D., and E. B. Cohen, M.D.,* Minneapolis, Minnesota
Discussion: Giles Koelsche, M.D., Rochester, Minnesota

3:00—RECESS TO VISIT EXHIBITS

Chairman: S. H. Jaros, M.D., Scarsdale, New York
Assisting: C. R. K. Johnston, M.D., Cleveland, Ohio

3:30—Summer Blooming Lamb's Quarter: A Factor in Inhalant Allergy

Johnny A. Blue, M.D., Oklahoma City, Oklahoma
Discussion: T. R. Stemen, M.A., Botanist, Oklahoma City, Oklahoma

3:50—Ocular Allergies

Justin M. Donegan, M.D.,* Chicago, Illinois

4:20—Sensitivity of Human Leukocytes from Tubercular and Nontubercular Individuals

Herbert Hall, M.S.,* and Morris Scherago, D.V.M., Lexington, Kentucky
Discussion: Harold A. Abramson, M.D., New York, New York

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*By invitation

4:40—Radioactive Iodine in the Treatment of Severe Chronic Pulmonary Emphysema

ALLAN HURST, M.D., MORRIS N. LEVINE, M.D.,* and D. RUSSELL RICH, M.D.,* Denver, Colorado

Discussion: EDWIN R. LEVINE, M.D.,* Chicago, Illinois

6:00—COCKTAIL HOUR—Terrace Casino

(Courtesy of the Schering Corporation)

7:00—BANQUET, ENTERTAINMENT, DANCING (Dress optional)—Terrace Casino

(Wine—Courtesy of the Nepera Chemical Company)

FRIDAY, APRIL 29, 1955

Morning Session—Constitution Room

Chairman: ORVAL R. WITHERS, M.D., Kansas City, Missouri

Assisting: CARL D. MARSH, M.D., Memphis, Tennessee

9:00—The Parent's Role in Allergic Management

CLIFFORD H. KALB, M.D., Milwaukee, Wisconsin

Discussion: MORRIS A. KAPLAN, M.D., Chicago, Illinois

9:20—C-Reactive Protein in Bronchial Asthmatic Patients

ABE L. AARONSON, M.D., M. A. KAPLAN, M.D., M. GOLDIN, M.S.,* and A. LIBRETTI, M.D.,* Chicago, Illinois

Discussion: HAROLD S. TUFT, M.D., Denver, Colorado

9:40—The Use of Oral Theophyllin Compounds in the Prophylactic Treatment of Bronchial Asthma

ETHAN ALLAN BROWN, M.D., and ROBERT E. CLANCY, M.D., Boston, Massachusetts

Discussion: LEON UNGER, M.D., Chicago, Illinois

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*By invitation

10:00—RECESS TO VISIT EXHIBITS

Chairman: JOHN GILLASPIE, M.D., Boulder, Colorado
Assisting: LESTER BARTLETT, M.D., Pittsburgh, Pennsylvania

10:30—Psoriasis—A New Approach

HOMER E. PRINCE, M.D., and RICHARD L. ETTER, M.D., Houston, Texas
Discussion: R. DALE DICKSON, M.D., Topeka, Kansas

11:00—Adjunctive Penicillin Prophylaxis for Bacterial Allergy—A Preliminary Report

VICTOR L. SZANTON, M.D.,* Ansonia, Conn.; H. COHEN, M.D.,* New York, N. Y., and HOWARD G. RAPAPORT, M.D., New York, N. Y.
Discussion: M. MURRAY PESHKIN, M.D., New York, N. Y.

11:30—Medico-legal Aspects of the Practice of Allergy

ELOI BAUERS, Executive Vice President and Counsel, American College of Allergists, Minneapolis, Minnesota

12:30—LUNCHEON—Ophtho-Otolaryngologic Allergy Panel—Grand Ballroom

Chairman and Moderator: FRENCH K. HANSEL, M.D., St. Louis, Missouri
Panel Members: MARTIN L. HARSHMAN, M.D., Lafayette, Indiana
JOHN D. MADDOX, M.D., Joplin, Missouri
F. LAMBERT MCGANNON, M.D., Lakewood, Ohio

FRIDAY, APRIL 29, 1955

Afternoon Session—Constitution Room

Chairman: GILES A. KOELSCHE, M.D., Rochester, Minnesota

Assisting: J. WARRICK THOMAS, M.D., Richmond, Virginia

2:00—Presidential Address

HOMER E. PRINCE, M.D., Houston, Texas

2:20—Introduction of LAWRENCE J. HALPIN, M.D., President-Elect, Cedar Rapids, Iowa

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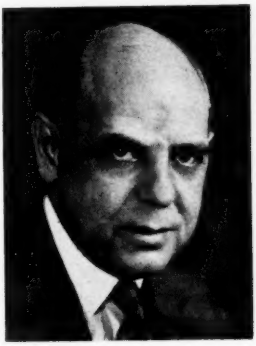
*By invitation

2:30—Medical Research in the Field of Allergy



Guest Speaker

ROBERT A. COOKE, M.D.,* Director, Institute of Allergy, Roosevelt Hospital, New York, New York

3:30—RECESS TO VISIT EXHIBITS

4:00—Business Meeting†—Constitution Room

FRIDAY, APRIL 29, 1955

Evening Session—Constitution Room

DERMATOLOGY SESSION

Chairman: A. ROSTENBERG, JR., M.D., Chicago, Illinois

8:00—Sectional Business Meeting

8:10—Overtreatment Dermatitis
L. EDWARD GAUL, M.D., Evansville, Indiana

8:30—Hand Eczemas; Classification, Pathogenesis and Therapy
SAMUEL M. BLUEFARB, M.D.,* Chicago, Illinois

8:50—Allergic Vasculitis
FREDERICK SZYMANSKI, M.D.,* Chicago, Illinois

9:10—Recent Studies in the Relationship Between Emotions and Atopic Dermatitis
MILTON ROBIN, M.D.,* and JOSEPH G. KEPECS, M.D.,* Chicago, Illinois

9:30—The Therapy of Allergic Dermatoses
JOHN B. HAEBERLIN, JR., M.D.,* Chicago, Illinois

9:50—Summary and Comment

OR

*By invitation

†Notice to all Fellows of the College: Since there is a conflict in the Bylaws defining the duties and powers of the Board of Directors and Board of Regents, respectively, an amendment will be proposed for the purpose of defining and limiting the powers and duties of the Board of Directors.

FRIDAY, APRIL 29, 1955

PSYCHOSOMATIC SESSION

Evening Session—Walnut Room

Chairman: HYMAN MILLER, M.D., Beverly Hills, California

8:00—Sectional Business Meeting

8:10—1. The Diagnostic and Therapeutic Value of the Initial Interview (Walnut Room)

Demonstrated on tape recording by JOHN H. MITCHELL, M.D., Columbus, Ohio

2. Directed Psychotherapy in Allergy (Parlor E)

HAROLD A. ABRAMSON, M.D., New York, New York

3. Psychodiagnostic Play Session with an Asthmatic Child. Followed by an interview with the parents regarding indications for care (Parlor F)

Clinical presentation by DOROTHY BARUCH, Ph.D.,* Beverly Hills, California

4. Psychotherapeutic Group Session with Mothers of Allergic Children (Parlor G)

Clinical demonstration by HYMAN MILLER, M.D., Beverly Hills, California

SATURDAY, APRIL 30, 1955

Morning Session—Parlor C

OPHTHO-OTOLARYNGOLOGIC SESSION

Chairman: KENNETH CRAFT, M.D., Indianapolis, Indiana

9:00—Alevaire Inhalation in Treatment of Asthma, Sinusitis, Bronchitis and Bronchiectasis of Adults

JOSEPH B. MILLER, M.D., Mobile, Alabama
Discussion opened by: LEON UNGER, M.D., Chicago, Illinois

9:40—Food Sensitization as a Cause of Perennial Nasal Allergy

EUGENE DERLACKI, M.D., Chicago, Illinois
Discussion opened by: S. C. MISSAL, M.D., Cleveland, Ohio

10:20—RECESS TO VISIT EXHIBITS

10:50—Sectional Business Meeting

11:00—Nasal Surgery in the Presence of Allergic Sinusitis

SAM H. SANDERS, M.D., Memphis, Tennessee
Discussion opened by: JACK ANDERSON, M.D., New Orleans, Louisiana

11:40—Retinal Detachment Possibly Due to Stress, Parasympathotonia and Non-adaptation Syndromes

LELAND H. PREWITT, M.D., Ottumwa, Iowa
Discussion opened by: JOHN MITCHELL, M.D., Columbus, Ohio

12:20—General Summary and Comments

*By invitation

SATURDAY, APRIL 30, 1955

Morning Session—Constitution Room

PEDIATRIC SESSION

Chairman: ALBERT V. STOESSER, M.D., Minneapolis, Minnesota

9:00—Acute Anaphylactic Reactions to Cow's Milk
C. COLLINS-WILLIAMS, M.D., Toronto, Ontario, Canada

9:15—Anaphylaxis in Man—A Serious Problem
LLOYD S. NELSON, M.D.,* Minneapolis, Minnesota

9:30—General discussion of first two papers

9:40—Asthmatic Bronchitis—Follow-up Study in General Pediatric Practice
GEORGE A. WATSON, M.D., Durham, North Carolina

9:55—General Discussion

10:05—Evaluation of Phthalamquin Therapy in Asthmatic Children
SUSAN C. DEES, M.D., and CAROLYN C. HUNTLEY, M.D.,* Durham, North Carolina

10:20—General Discussion

10:30—RECESS TO VISIT EXHIBITS

11:00—Section Business Meeting

11:15—A Program of Education in Inhalant Avoidance
FREDERIC SPEER, M.D., Kansas City, Kansas

11:30—General Discussion

11:40—Not Everything That Wheezes Is Bronchial Asthma
BENNETT KRAFT, M.D., Indianapolis, Indiana

11:55—General Discussion

12:05—Two Hundred Pediatric Allergy Patients—A Statistical and Clinical Evaluation
ARTHUR A. GOLDFARB, M.D., New York, New York, and VICTOR SZANTON, M.D.,* Ansonia, Connecticut

12:20—General Discussion

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*By invitation

Eleventh Annual Congress

TO BE READ BY TITLE

Semantics in Allergy
K. A. Baird, M.D., Lancaster, New Brunswick, Canada

New Evidence Concerning Allergy to Bacterial Products
K. A. Baird, M.D., Lancaster, New Brunswick, Canada

The Treatment of Asthma in Patients with Active Pulmonary Tuberculosis
Hal M. Davison, M.D., Atlanta, Georgia

Alevaire Inhalations in the Treatment of Asthmatic Attacks and Chronic Asthma
D. Edward Frank, M.D., Sun Valley, California

Some Industrial Aspects of Inhalant Allergy
Lawrence J. Halpin, M.D., Cedar Rapids, Iowa

Barrier Creams in Allergic Dermatoses
S. H. Jaros, M.D., Scarsdale, New York

Seasonal Patterns in Aerobiological Populations
Marie B. Morrow, Ph.D., Austin, Texas; George H. Meyer, M.A., Austin, Texas; and Homer E. Prince, M.D., Houston, Texas

Bronchial Asthma—What Is It?
M. Murray Peshkin, M.D., New York, New York

Allergic Type Reactions to Chemical Additives and Contaminants of Foods and Biologicals
Theron G. Randolph, M.D., Evanston, Illinois

Alkali Therapy in Acute Allergy
Theron G. Randolph, M.D., Evanston, Illinois, and Harry G. Clark, M.D., Detroit, Michigan

Drugs in Asthma; Their Clinical Usefulness and Their Dangers
Jack A. Rudolph, M.D., Miami Beach, Florida

A Further Study on the Circulating Blood Levels of Certain Essential Metabolites in Infantile Bronchial Asthma
Nathan E. Silbert, M.D., J. E. Schneider, M.D., and H. E. Worne, Ph.D., Lynn, Massachusetts

Women's Auxiliary

THURSDAY, APRIL 28, 1955

9:00-12:00—First Annual Meeting of the Women's Auxiliary of the American College of Allergists, Inc.

12:00- 1:30—Luncheon for members of the Auxiliary

1:30- 2:30—Program for members of the Auxiliary

3:00- 5:00—Refreshment Hour. Tea, coffee and cookies will be served in the Hostess Room for *all* members of the College and their wives. (Courtesy of the Chicago Allergy Society)

6:00 —Cocktail Hour. (Courtesy of the Schering Corporation)

7:00 —Banquet, entertainment, dancing (dress optional)

FRIDAY, APRIL 29, 1955

11:30 —Luncheon and Tour of Art Institute of Chicago

3:00- 5:00—Refreshment Hour. Tea, coffee and cookies will be served in the Hostess Room for *all* members of the College and their wives. (Courtesy of the Chicago Allergy Society)

The Hostess Committee will maintain a Hospitality Room at the Morrison Hotel from Sunday, April 24, at 2:00 p.m. until the close of the convention on Saturday, April 30. Members of the Hostess Committee will be available for consultation and advice on shopping, restaurants, theatres, radio programs, et cetera.

Technical Exhibits

Almay Beauty Preparations, Division of Schieffelin & Co.	New York, New York
The Armour Laboratories	Kankakee, Illinois
The Borden Company	New York, New York
Brewer & Company	Worcester, Massachusetts
Bruce Publishing Company	St. Paul, Minnesota
Burroughs Wellcome & Co. (U.S.A.), Inc.	Tuckahoe, New York
Center Laboratories, Inc.	Port Washington, New York
The Chicago Dietetic Supply House, Inc.	Chicago, Illinois
Ciba Pharmaceutical Products, Inc.	Summit, New Jersey
The Coca-Cola Company	Atlanta, Georgia
Joseph K. Dennis Co.	Chicago, Illinois
The DeVilbiss Company	Somerset, Pennsylvania
Doho Chemical Corporation	New York, New York
Dome Chemicals, Inc.	New York, New York
Duke Laboratories	Stamford, Connecticut
Eisele & Company	Nashville, Tennessee
Encyclopaedia Britannica	Chicago, Illinois
Endo Products, Inc.	Richmond Hill, New York
E. Fougera & Co., Inc.	New York, New York
Gerber Products Company	Fremont, Michigan
Graham Laboratories	Dallas, Texas
Hollister-Stier Laboratories	Philadelphia, Pennsylvania
Irwin, Neisler & Co.	Decatur, Illinois
Lide Labs., Inc.	St. Louis, Missouri
Eli Lilly and Company	Indianapolis, Indiana
Loma Linda Food Company	Arlington, California
Luzier's, Inc.	Kansas City, Missouri
Marcelle Cosmetics, Inc.	Chicago, Illinois
McNeil Laboratories, Inc.	Philadelphia, Pennsylvania
Mead Johnson & Co.	Evansville, Indiana
Nepera Chemical Co., Inc.	Yonkers, New York
Pfizer Laboratories	Brooklyn, New York
Ralston Purina Company	St. Louis, Missouri
Raytheon Manufacturing Company	Waltham, Massachusetts
A. H. Robins Co., Inc.	Richmond, Virginia
Sandoz Pharmaceuticals	New York, New York
Schering Corporation	Bloomfield, New Jersey
G. D. Searle & Co.	Chicago, Illinois
Sharp & Dohme	Philadelphia, Pennsylvania
Sharp & Sharp	Everett, Washington
Smith, Kline & French Laboratories	Philadelphia, Pennsylvania
Stemen Laboratories, Inc.	Oklahoma City, Oklahoma
Travenol Laboratories, Inc. (Subsidiary of Baxter Laboratories, Inc.)	Morton Grove, Illinois
United States Tobacco Company	New York, New York
The Upjohn Company	Kalamazoo, Michigan
Westwood Pharmaceuticals	Buffalo, New York
Winthrop-Stearns, Inc.	Philadelphia, Pennsylvania

PRESIDENTIAL ACCEPTANCE ADDRESS

HOMER E. PRINCE, M.D., F.A.C.A.

Houston, Texas

AS I enter the highest elective office you can bestow on any member of this Society, I am beset with conflicting emotions. Let me assure you that the honor makes this occasion the happiest moment of my life. This manifestation of your confidence obligates me to serve the College, and through it, allergists everywhere, to the very best of my ability. I accept this obligation.

To one who has worked with the American College of Allergists since its inception, it is a matter of no small satisfaction to observe its growth to its position of influence throughout the world of allergy. This robust organization has attained substantial maturity in twelve short years because of adherence to the unyielding principles upon which it was established, namely, encouragement to the younger men in allergy, and advancement of the specialty of allergy in general. The many aspects of allergy presented in this week's program should be a source of pride and a tribute to the foresight of the founders of the College as well as an inspiration to the newest members.

One of the most intriguing aspects of the practice of allergy is the fact that it constantly presents new problems for study and solution. I can remember when many patients with respiratory allergy could be placed in the categories of sensitization to pollens, a few inhalants and commonly eaten foods. Now the problems of allergy are much more complex. What is the cause of this trend? The characteristic patient response certainly has not varied. But we are living in a changing era with shortened distance and time barriers; an era of industrialization not only in urban centers but in rural areas as well; an era literally of accelerated and different modes of living.

Patients no longer spend all of their time under static environmental conditions. I recently treated a pollen-sensitive patient who regularly spent one day a week in New Mexico, two in Wyoming, and his weekends in Houston, in addition to an occasional trip to Mississippi or Louisiana. To just what pollens he was exposed along with the dozen with which I treated him I will never know.

A few years ago I began to encounter an unusual source of house dust exposure. "Television asthma" is the term I now apply to symptoms arising from dust exposure in daybeds, divans, overstuffed chairs, hassocks or pillows which many patients insist on crowding into the rooms where they spend much time viewing their television sets.

Presidential Acceptance Address, Decennial Congress, The American College of Allergists, April 9, 1954, Miami Beach, Florida.

Our ever-expanding manufacturing and chemical industries contribute not only to an alarming atmospheric pollution but provide unusual hazards to employes for respiratory and dermatologic allergy. Many modern chemical substances such as DDT, the plastics, the resins, synthetic fibers, and some of our wonder drugs, occasionally become powerful allergens. Psychologically, our way of life itself is becoming so high-geared that many people cannot keep up with it, in spite of the fact that we have endangered, in the effort, among other things, the world's supply of coffee! As allergists we will have no particular difficulty in handling the patients with simple problems whose history alone often allows the family physician to offer the proper treatment; our major effort is required for the more complex and difficult cases.

Research in the fields of immunology, botany, mycology, bacteriology, chemistry and endocrinology has brought forth new hypotheses, new causative agents and, as well, new methods of treatment. All of these must be correlated and evaluated in that laboratory of crucial experiment, the response of the allergic patient. We as allergists—I ask you who can better perform this task—must make our appraisals and our decisions as unbiased clinicians, avoiding the pitfalls of enthusiasm, shunning the spectacular, and always and ever seeking the truth.

Although more potent drugs are constantly becoming available, every allergist knows that symptomatic control alone is not sufficient for the greater number of patients with allergic disorders. We may consider the antihistaminic drugs alone. Relief of some allergic symptoms by these preparations has been spectacular, but in many instances temporary and to a noticeably diminishing degree. Consequently, patients dependent on this type of treatment must constantly seek newer compounds to replace the older which have lost their magic. The sad commentary I must make is that since the widespread use of antihistaminic agents for the treatment of hay fever I see an alarming increase in the numbers of patients suffering from bronchial asthma. All of these relate the same story, which in brief tells of unrestricted symptomatic treatment during the pollen seasons, until relief can no longer be obtained from increased doses of first one, then several additional, antihistaminic drugs. Furthermore, the indiscriminate use of even more powerful agents, such as ACTH and cortisone, for symptomatic relief only must be viewed with great concern. The true treatment of these patients must be on an immunologic basis.

But the well grounded allergist must go farther than immunology in his investigations and treatments. In this day of specialization—or, shall I say, over-specialization—in medicine, the allergist must remember that frequently he is the only physician to whom many of his patients can turn for advice on matters pertaining to other than strictly allergic problems. Reluctance on the grounds of ethics, or inability through ignorance, to render appropriate counsel could mean simply that his

allergic patient might not be warned in time to attend to some other trivial condition before it becomes serious. The full import of this situation has struck me forcibly when I have inquired of a new patient the name of his family physician. The answer is often, "You are, Doctor." What a responsibility at a time when general practitioners are scarcer than board certified specialists in all the branches of medicine and surgery!

What then are our duties as allergists? We have emerged from the role of "needle pushers" and are fundamentally physicians. Enriched by our special viewpoints and particular methods, the medicine we practice becomes a distinct science and an art. But we must remember that our patients are whole human beings, subject to diverse ailments, and they are not to be regarded merely as a set of wheezy bronchial tubes, a troublesome nose, an eczematous skin or an upset digestive tract. We must employ accepted principles of the science of medicine in building up and maintaining the general health of those allergic patients whose care is entirely in our hands. We dare not overlook adequate nutrition and hemoglobin levels, normal endocrine relationships, proper physiologic function, common sense psychosomatic balance, and the coexistence of other diseases as we manipulate specific immunologic factors. In short, it is our privilege to be Doctors of Medicine and work for the welfare of our patients and to the glory of God through the advantages of our special training as allergists.

I ask your co-operation and help to the end that we can individually and as a group measure up to everything expected of us as allergists and that we may work together in harmony with a zealous devotion to our common welfare, the betterment of allergy.

PHARMACOLOGIC STUDIES ON A NEW ANTIHISTAMINE† AND ITS COMBINATION WITH CALCIUM

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Basle, Switzerland

ALTHOUGH a large number of antihistaminic preparations are used today, they have not entirely replaced medications previously used in treating allergic disturbances. Clinical experience has shown that their therapeutic value is contingent not only on the antagonism towards histamine, but also on other less specific actions (e.g. anticholinergic, local anesthetic, central and capillary permeability). Nonspecific therapy of allergic disturbances, therefore, has received renewed interest. Calcium therapy also plays an important role in the treatment of allergic conditions.

TABLE I.

Antihistaminic Agents	LD_{50} i.v. in mg/kg in:			
	Mouse	Rat	Guinea Pig	Rabbit
1-methyl-4-amino-N'-phenyl-N'-(2'-thenyl)-piperidine-tartrate	58	64	56	31
Pyranisamine	24	—	27	14.4
Tripelenamine[2,7]	16	13	—	10
N'-(2-pyridyl)-N'-(3-thenyl)-N,N-dimethylethylendiamine[7]	14.2	15	—	12
N-dimethylaminoethyl-N-p-chlorbenzyl-α-amino-pyridine HCl[1]	45	30.5	—	14.6
Diphenhydramine[4,7]	35	42	—	10
Metaphenilen[3]	45	—	30	30
Phenindamine[10]	22.5	—	—	15

In an effort to derive therapeutic benefit from the different mechanisms of action of both calcium and the antihistaminics, we have attempted to add an acceptable antihistaminic to calcium gluconogalactogluconate (Neo-Calglucon), a calcium salt which has been in clinical use for many years. Pharmacologic study resulted in the choice of 1-methyl-4-amino-N'-phenyl-N'-(2-thenyl)-piperidine tartrate (Sandostene) as an antihistaminic. We are reporting our results on the pharmacologic properties of this compound, both alone and in combination with calcium. A mixture (ASC 16*), incorporating in each cc 5 mg of the antihistamine and 9 mg of ionized calcium in form of calcium gluconogalactogluconate (Neo-Calglucon), was used.

TOXICITY STUDIES

The intravenous LD 50 in various animals is presented in Table I together with a comparison of other antihistaminic substances. It is evident that the acute intravenous toxicity of the antihistamine is below

From the Pharmacology Laboratory Sandoz Ltd., Basle, Switzerland.

†1-methyl-4-amino-N'-phenyl-N'-(2-thenyl)-piperidine tartrate.

*ASC 16—laboratory designation for Sandostene+Calcium.

that of a number of compounds now in common use. This applies also to its chronic toxicity, since daily subcutaneous injections of 30 mg/kg are tolerated by guinea pigs for an entire month without evidence of any organ pathology. Administration of 69 mg/kg subcutaneously for thirty

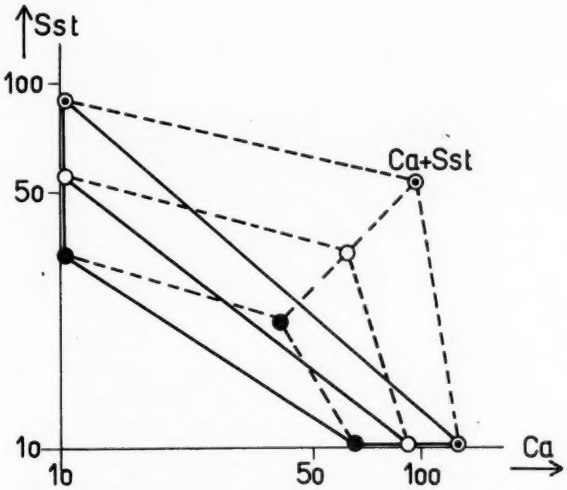

Fig. 1. This illustration is based on the calculated dose-effect curves for calcium, the antihistamine and for the combination ASC 16. The black circles indicate the maximal tolerated dose (LD_0). The blank circles indicate the LD_{50} and the dotted circles indicate the LD_{100}. The abscissa shows the amount of calcium salt and the ordinate the amount of antihistamine (mg/kg) in logarithmic scale. Were the LD's of calcium salt and antihistamine on an additive basis, these points would lie on the diagonals. However, as shown by the dashed line, the LD's of the combination material is well above the expected value.

days resulted in death of 50 per cent of the animals. In comparison, a similar lethality rate was produced by 38 mg/kg of pyranisamine subcutaneously.

The combined administration of calcium and antihistamine is well tolerated: Guinea pigs survived doses of 4 to 5 cc/kg intravenously of a solution containing 5 mg of the antihistamine and 9 mg of the calcium salt per cc. Repeated subcutaneous administration of this mixture continued for one month indicated the LD 50 was a total of 10.8 cc/kg. A comparison of the toxicities of the two components alone and in combination, indicates clearly that the toxicities are not additive but that the two agents mutually increase their individual tolerances. The sum total of the toxic effect of the combination is significantly lower than might be expected were the proportionate toxicities of the two components added together (Fig. 1). On the basis of dose-effect curves, it can be calculated that

TABLE II. EFFECTIVE CONCENTRATIONS OF SEVERAL ANTIHISTAMINIC AGENTS IN INHIBITING HISTAMINE ON THE ISOLATED SMALL INTESTINE OF THE GUINEA PIG

Antihistaminic Agents	Gm/cc
1-methyl-4-amino-N'-phenyl-N'-(2'-thenyl)-piperidine tartrate	2×10^{-9}
Pyranisamine[3]	1×10^{-9}
Diphenhydramine[3]	3×10^{-9}
Antazolin[3]	0.7×10^{-7}
N-dimethylaminoethyl-N-p-chlor-benzyl-α-aminopyridine HCl[1]	2×10^{-9}

the additive effects of the simultaneous administration of 37 mg of the calcium salt and 20.5 mg of the antihistamine/kg should kill 50 per cent of the animals. Actually, this is achieved with 64 mg/kg calcium and 35 mg/kg of the antihistamine intravenously, thus indicating that in combination approximately 70 per cent more of the two components can be administered.

Lethal doses of the drug will kill rabbits within a few minutes. If, however, the same lethal doses are given together with the calcium salt, the animals will survive from twelve to twenty-four hours, indicating that calcium exercises a "detoxifying" effect. Conversely, the antihistamine appears to be able to inhibit or suppress undesirable effects of the calcium ion. Cardiac arrhythmias frequently appear in control animals when larger doses (50 to 70 mg calcium/kg per minute) of calcium salts are administered rapidly intravenously. These cardiac disturbances do not occur if calcium is administered in combination with the antihistamine.

In summary, toxicity studies show that Sandostene can be classified as one of the less toxic antihistaminics, and that its tolerance is further increased by combination with calcium.

STUDIES ON HISTAMINE ANTAGONISM

The inhibitory effect of this drug on histamine was studied by various tests.

1. Isolated guinea pig ileum: indicating that the antihistamine produces typical histamine antagonism in very high dilutions (Table II and Fig. 2).

2. Isolated arterial strips: doses needed to produce frank inhibition are from 50 to 100 times smaller than the effective histamine dose.

3. Bronchial spasm (cat)[9] produced by intravenous injection of 5 to 20γ of histamine can be prevented by the previous administration of the drug in doses of 0.03 mg/kg and upward.

4. Wheal (rabbit skin) produced by 10γ of histamine intracutaneously is completely inhibited by administration of 5.5 mg/kg of the antihistamine intravenously.

5. Depressor effect of histamine 5γ/kg intravenously (cat) is modified by 0.1 to 0.3 mg of the drug intravenously. For complete inhibition 0.5 to 1 mg/kg is required. In the rabbit, histamine antagonism on blood

pressure is less marked and from 3 to 5 mg of the antihistamine are therefore required for complete inhibition.

6. *Histamine Detoxification*—Administration of 0.05 to 0.07 mg/kg of the drug to guinea pigs will protect 50 per cent of the animals against

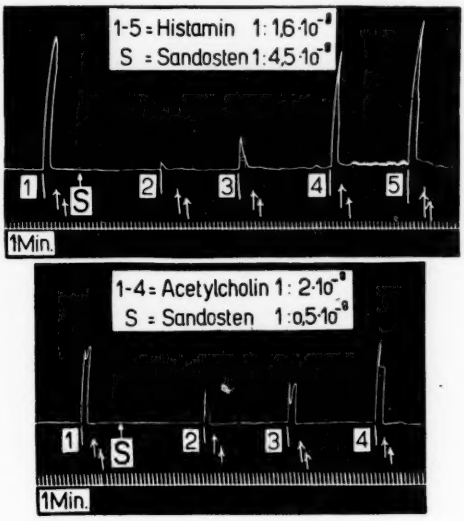

Fig. 2. Isolated guinea pig ileum: inhibition of histamine (above) and inhibition of acetylcholine effect (below) by 1 methyl-4-amino-N′-phenyl-N′-(2-thenyl)-piperidine tartrate.

a 100 per cent lethal dose of histamine (8.8 mg/kg subcutaneously). Pre-treatment of the animals with 20 mg/kg of the antihistamine subcutaneously indicates that 50 X LD 100 (440 mg/kg histamine subcutaneously) has to be injected to kill 50 per cent of the animals. Even a 100 X LD 100 (880 mg of histamine subcutaneously) was survived by 27 per cent of the animals pre-treated with the drug.

The sum of all the above-mentioned results indicates that this substance specifically inhibits the manifold effects of histamine and assumes an intermediate position concerning antihistaminic potency within the series of available antihistaminic substances. The addition of calcium in the ratio present in ASC 16 does not significantly alter the antihistaminic effect of this product; in other words, the histamine antagonism is not increased or reduced. Since the therapeutic effect of an antihistaminic agent is not dependent only on absolute histamine-inhibitory effectiveness, therefore clarification of other pharmacodynamic properties is necessary.

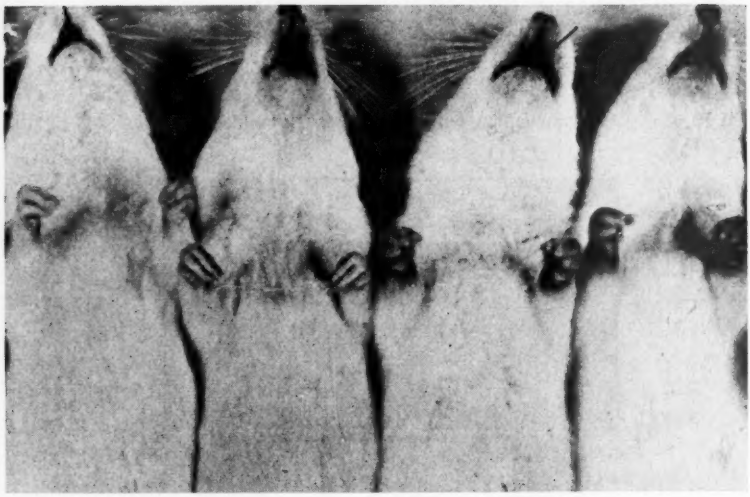

Fig. 3. Intravenous injection of Trypanblue into dextran pre-treated rats produces intensive coloration of the edematous parts. The illustration on the right shows two such animals with swollen paws and snouts. The two animals on the left protected by the antihistamine received the same amount of dextran and Trypanblue. Swelling and exudation of the dye did not occur in these animals.

TABLE III. EFFECTIVE CONCENTRATIONS OF SEVERAL ANTIHISTAMINIC AGENTS IN INHIBITING ACETYLCHOLINE ON THE ISOLATED SMALL INTESTINE OF THE GUINEA PIG

Antihistaminic Agents	Gm/cc
1-methyl-4-amino-N'-phenyl-N'-(2'-thenyl)-piperidine tartrate	1×10^{-8}
Pyranisamine[3]	5×10^{-6}
Diphenhydramine[3]	5×10^{-8}
Antazolin[3]	2×10^{-6}
N-dimethylaminoethyl-N-p-chlor-benzyl-α-aminopyridine HCl[1]	practically ineffective

STUDIES ON OTHER PHARMACOLOGIC PROPERTIES OF 1-METHYL-4-AMINO-N'-PHENYL-N'-(2-THENYL)-PIPERIDINE TARTRATE

Acetylcholine Antagonism.—Antihistaminics may inhibit acetylcholine effects. Most of them do so, however, in doses exceeding their therapeutic range. A well-defined anticholinergic action may in no way be considered a side effect, but rather a desirable action of the drug, since acetylcholine apparently plays an important role in allergic reactions and may be responsible for the development of autonomic disturbances associated with allergy. It is evident from Figure 2 and Table III that this antihistamine possesses distinct anticholinergic properties. Examination of this effect on the ileum and seminal vesicle of the guinea pig shows that weight for weight the substance is approximately 50 to 100 times weaker than atropine. However, considering that it is given therapeutically in doses fifty to one

hundred times higher than atropine, it may be assumed that its anticholinergic properties may well be manifested.

Adrenalin Antagonism.—Adrenergic mechanisms are inhibited by concentrations of the drug between 10^{-5} and 10^{-6}. On the isolated seminal vesicle of the guinea pig and rabbit uterus, it was 300 to 500 times weaker than ergotamine.

Local Anesthetic Action.—Most antihistaminics possess some local anesthetic effects. The product involved was tested on the rabbit cornea and its topical local anesthetic effect was found to be superior to that of procaine.

Spasmolytic Action.—This antihistamine does not possess any typical papaverine-like spasmolytic action. Contraction of the isolated guinea pig ileum produced by barium chloride may nevertheless be inhibited by it in concentrations of 0.2 to 1 X 10^{-5}. In comparison, contractions of the isolated ileum produced by histamine or acetylcholine are inhibited in concentrations in the order of 10^{-8}. Spasms of the test organ due to anaphylaxis (administration of egg albumin to sensitized guinea pigs) can be inhibited by this drug in concentration ranges of 1:10 million to 1:200 million.

STUDIES ON CAPILLARY PERMEABILITY

Part of the therapeutic effect of the antihistaminics is manifested in decreasing capillary permeability. For this reason the antihistamine was submitted to thorough examination concerning its effect on capillary permeability by means of various tests.

Dextran Induced Edema in the Rat.—Rats pre-treated with dextran are suitable test animals for studying substances inhibiting capillary permeability. As shown by Morrison et al,[11] certain antihistaminics inhibit the characteristic dextran edema whereas other antihistaminics do not exhibit this effect. One cc per 100 gm body weight, dextran is administered intraperitoneally in rats in a 6 per cent solution. Within a short time a marked edema, particularly of the snout and paws, develops. Plethysmographic recording of the volume increase of the paw is a suitable indicator and shows that the compound under discussion is capable of inhibiting the development of dextran edema in the great majority of cases (Table IV and Fig. 4). In comparison, other antihistaminics do not show this effect or, if they do, they are considerably less active. Even 1-methyl-4-amino-N'-benzyl-N'-phenyl-piperidine-di-chlorhydrate which is chemcally closely related to the substance involved is considerably less effective.

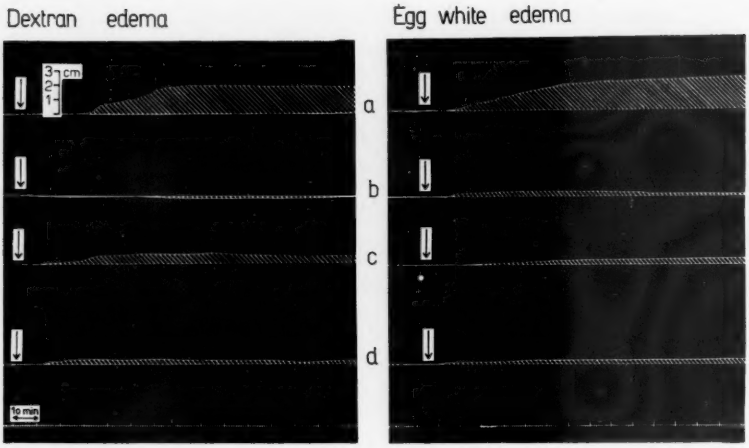

Fig. 4. Plethysmographic record of rat paw volume following injection of dextran and egg albumin. Each illustration represents four animals whereby "a" is a control and the other three ("b," "c," "d") were pre-treated with 10 mg/kg) of the antihistamine intravenously. The figures indicate distinctly the absent or very slight increase in paw volume in the antihistamine treated animals.

TABLE IV. INHIBITION OF DEXTRAN EDEMA AND EGG ALBUMIN EDEMA IN THE RAT

	Dextran			Egg Albumin		
	Control without pre-treatment	1-methyl-4-amino-N'-benzyl-N'-phenyl-piperidine-dichlorhydrate	1-methyl-4-amino-N'-phenyl-N'-(2'-thenyl)-piperidine-tartrate	Control without pre-treatment	1-methyl-4-amino-N'-benzyl-N'-phenyl-piperidine-dichlorhydrate	1-methyl-4-amino-N'-phenyl-N'-(2'-thenyl)-piperidine-tartrate
Number of Animals	33	39	32	7	22	24
Without Edema	—	12	24	—	—	—
With Edema	33	27	8	7	22	24
Mean % Increase of Paw Volume	42%	23%	7%	46%	19%	8.3%

Egg Albumin Edema in the Rat.—The marked inhibition of capillary permeability by the antihistamine can also be shown in this form of edema. After injection of 0.1 cc of a 20 per cent egg albumin solution under the skin of the paw, marked swelling is elicited within forty to sixty minutes. Animals pretreated with the drug show only slight increase of paw volume. (Fig. 4 and Table IV). In this experiment also, 1-methyl-4-amino-N'-phenyl-N'-(2-thenyl)-piperidine tartrate is approximately three and a half to four times more effective than 1-methyl-4-amino-N'-benzyl-N'-phenyl-piperidine.

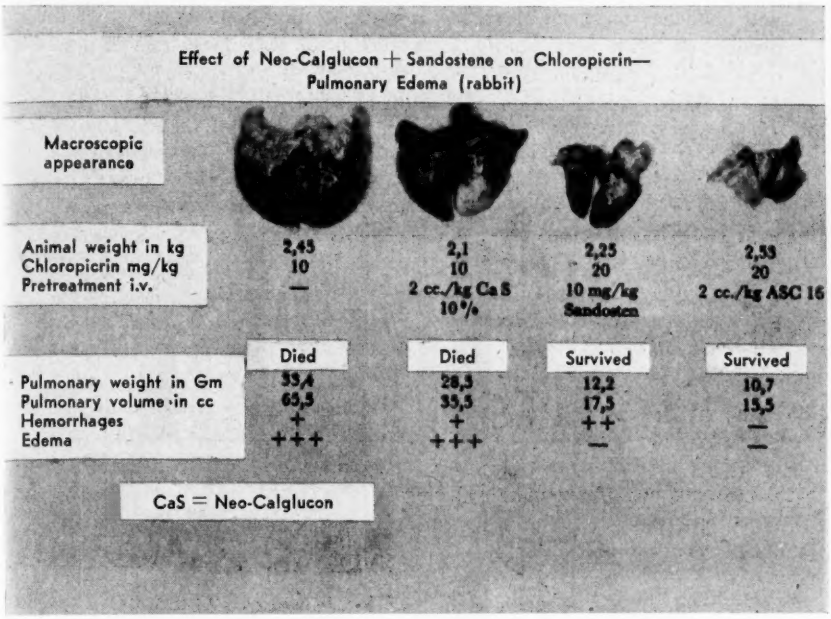

Fig. 5. Chloropicrin injection increases the weight and volume of the rabbit lung four to five times. Calcium alone is ineffective; the antihistamine and even more a combination of the calcium salt with the antihistamine markedly inhibits the development of pulmonary edema. Pre-treated animals live longer and may even survive the administration of chloropicrin.

TABLE V. CHLOROPICRIN EXPERIMENTS IN RABBITS

Pretreatment	Number of Animals in Experiment	Time of Death			Total Died	Survived
		Within 1 hr.	1-6 hrs.	12-24 hrs.		
None (control animals)	8	5	3	0	8	0
18 mg/kg calcium i.v. (calcium gluconogalactogluconate)	7	4	2	0	6	1
10 mg/kg Sandostene i.v.	20	2	3	7	12	8
10 mg/kg Sandostene and 18 mg/kg calcium i.v. (2 cc/kg ASC 16)	23	3	3	3	9	14

Chloropicrin Pulmonary Edema in the Rabbit.—Intravenous injection of 10 to 15 mg/kg of chloropicrin produces a massive hemorrhagic pulmonary edema which is uniformly lethal.[6] Pretreatment with the antihistamine significantly inhibits the development of this edema and reduces lethality by one-half (Table V and Fig. 5).

Sodium Chloride Hypertension in Rat.—Chronic administration to white rats of a diet containing 2 per cent sodium chloride produces increase of blood pressure.[12] In addition, symptoms of peripheral vascular disturbances

with tendency to edema develop. In view of the inhibitory effect of the product on tissue permeability, tests were made with these rats to determine whether treatment could be accomplished. It was shown that in spite of continued administration of sodium chloride, the animals lose weight

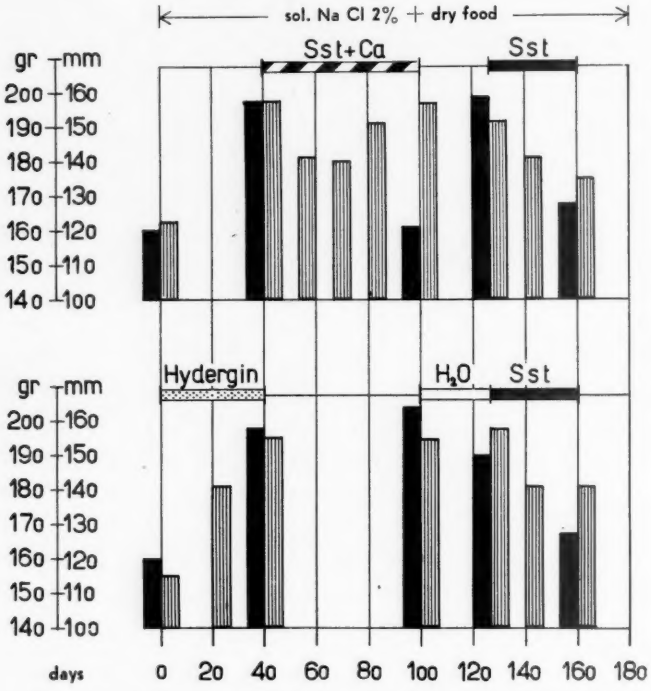

Fig. 6. This illustration shows the changes in blood pressure (black bar) and of the body weight (shaded bar) of two groups of ten rats each following administration of 2 per cent sodium chloride in the diet. Within forty days, blood pressure and body weight increased significantly. This occurs also in animals treated daily with Hydergine (vasorelaxant hydrogenated ergot alkaloids). The antihistamine (15 mg/kg by mouth) alone and in combination with calcium will lower the elevated blood pressure and transiently reduce the increase in body weight.

and even blood pressure decreases (Fig. 6). Administration of similar doses of the drug to control animals does not alter their body weight curves. The administration of a placebo solution does not influence blood pressure or body weight of sodium chloride hypertensive animals. The results of these experiments may be related to the marked effect of the antihistamine in lowering tissue permeability and present interesting aspects of the pathogenetic mechanisms of sodium chloride hypertension.

The mechanism of the tissue permeability inhibiting effect of this product can so far not be explained exactly. It is known that antihistaminics have

constrictor effects on pre-capillary sphincters and thus can eliminate from circulation large portions of the capillary net.[5] Whether Sandostene exercises its antiedematic effect by a similar mechanism or whether other factors are also involved is not known at the present time. Interesting in this respect are the results of the combined administration of the antihistamine and the calcium salt. Studies in man have shown much more intensive inhibition of the permeability of the anterior eye chamber when both substances were given together.[8] In our animal experiments, similar observations were made with chloropicrin in the rabbit (Table V). In regard to the dextran edema of the rat, the calcium salt alone is considerably less effective than in combination with the antihistamine. On the other hand, the calcium antihistamine combination is considerably less protective than the antihistamine alone. Initial experiments seemed to indicate the reverse. However, larger series of experiments proved the distinct superiority of the antihistamine alone over the combination product. Apparently, the underlying mechanisms vary considerably in the different edema forms. Correspondingly, the effects of one or the other of the two compounds is manifested more or less. The high permeability reducing activity of 1-methyl-4-amino-N′-phenyl-N′-(2-thenyl)-piperidine tartrate alone and in combination with calcium would seem to indicate broad therapeutic application.

SUMMARY

A new antihistaminic, 1-methyl-4-amino-N′-phenyl-N′-(2-thenyl)-piperidine tartrate (Sandostene), is subject to pharmacologic analysis both alone and in combination with a calcium salt. The main findings are as follows:

1. Low toxicity which further is decreased when combined with the calcium salt.

2. Marked histamine antagonism associated with anticholinergic and local anesthetic properties.

3. Inhibitory effect on tissue permeability manifested in various forms of experimental edema.

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AEROSOLS OF EPOXYTROPINE TROPATE METHYLBROMIDE FOR THE RELIEF OF BRONCHOSPASM

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THE ideal therapeutic agent for the relief of the asthmatic paroxysm, in addition to being an effective bronchodilator, should have antihistaminic and anticholinergic properties.[10] In pathophysiologic studies of bronchial asthma the autonomic nervous system and acetylcholine have been implicated by many investigators. Eppinger and Hess described bronchial asthma as a condition of "pathological vagotonia" an abnormal preponderance of vagal tone.[3] Other investigators subsequently demonstrated that acetylcholine was involved in the pathogenesis of bronchial asthma. In 1937 Kallos and Pagel produced asthmatic paroxyms in guinea pigs with the administration of aerosols of acetylcholine.[6] Moll reported that the subcutaneous administration of acetyl-beta-methylcholine to asthmatic subjects induced severe bronchospasm which was "indistinguishable" from a spontaneous attack of bronchial asthma.[9]. Similar observations have been made by other groups of investigators.[1,2,5]

A considerable number and variety of anticholinergic agents have been evaluated in our laboratory. Anticholinergic potency and effect on induced bronchospasm in asthmatic subjects were evaluated by the means of the protection study technique[8] as well as by clinical testing. Studies were made with atropine sulfate, bellafoline, scopolamine hydrobromide and methantheline bromide (Banthine®).[1,5] Although favorable results were noted with these agents in our laboratory, they proved to be of limited value in the actual management of the patient with bronchial asthma. The drying effect of most of these agents upon the bronchial secretions was considered harmful.

The adrenergic bronchodilator aerosols are particularly effective agents when properly used. For routine administration usually two to six hand bulb inhalations with the Vaponefrin nebulizer suffice for relief. For the relief of the acute paroxysm and in the more seriously ill chronic asthmatic state, these agents are generally employed in dosage of 0.5 to 1.0 cc with the use of the air pump or oxygen tank technique. These aerosols may stimulate the central nervous and cardiovascular systems in sensitive patients or when used too often and to excess; manifestations of shakiness,

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nervousness, palpitation, headaches and tachycardia may be noted in these instances. For some time there has been a search for a therapeutic aerosol which can achieve some degree of bronchodilatation devoid of undesirable side effects.

It is the purpose of this report to describe our studies with aerosols of a new anticholinergic agent, Pamine®* (Epoxytropine tropate methylbromide), which appears to be effective in relieving the bronchospasm and dyspnea of an asthmatic attack. Our observations also indicate that the bromide has little effect on physiologic systems other than bronchiolar muscle when given by aerosol. In a series of gastric antisecretory compounds under investigation, its oral administration was found to be one of the most effective adjuncts with the least troublesome reactions.[7]

TECHNIQUES FOR EVALUATING BRONCHODILATOR POTENCY

1. The potency of a bronchodilator agent may be measured in man by estimation of the degree of protection it confers against the drop in vital capacity which may be induced at will in sensitive asthmatic individuals by the administration of histamine or methacholine. The technique of these protection studies has been described in detail elsewhere.[8]

2. The vital capacity and maximal breathing capacity measurements taken before and after the administration of the bronchodilator agent may also serve as criteria of the drug's effectiveness and are most valuable if repeated over a period of several days.[4] In most cases the readings taken immediately before and after the administration of a drug offer an objective comparison of its effectiveness.

PRESENT STUDY

1. Protection Studies.—A solution of methylbromide, 0.33 mg in 1.0 cc of saline, was administered as an aerosol to five patients and tested to determine what protection was afforded against the bronchospastic effects of intravenous methocholine. The protection afforded against the induced bronchospasm was very significant and, moreover, was of good duration in all five patients (Fig. 1).

2. Ventilatory Studies.—The bronchodilator potency of the bromide is appreciable even when the patient himself is not aware of bronchospasm. The term "bronchospasm" is used to denote the narrowing of the bronchi and bronchioles which leads to the difficulty in breathing manifested by typical wheezes and rhonchi and by prolonged expiration.

One cc containing 0.33 mg of the aerosol was administered to seventy-nine patients with chronic bronchial asthma with a degree of bronchospasm ranging from 1+ to 3+ in intensity. To sixty-eight of these patients the aerosol was administered with a conventional Vaponefrin nebulizer. Oxy-

*Kindly supplied by the Upjohn Co., Kalamazoo, Michigan.

gen flows of 4 to 5 liters per minute were sufficient to aerosolize the one cc of solution in ten minutes. Vital capacity and maximal breathing capacity measurements were made before and after the administration of the aerosol and repeated after the additional administration of one cc of

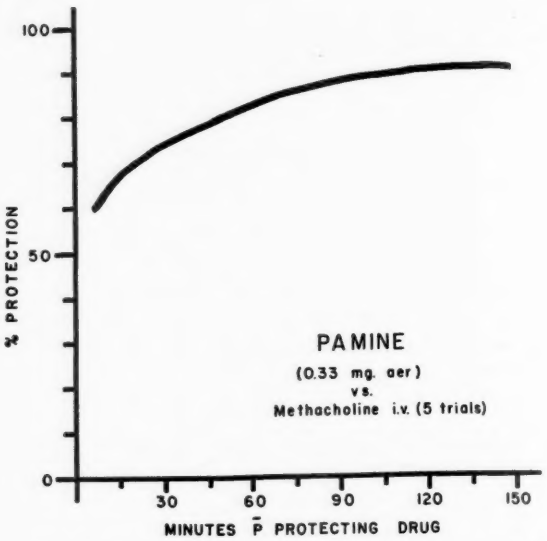

Fig. 1. The protecting capacity of Pamine, 0.33 mg, given by aerosol, against the bronchospastic effects of intravenous methacholine.

Isuprel® aerosol (isopropylarterenol hydrochloride) 1:200 concentration.

Improvement in vital capacity and maximal breathing capacity after the administration of Pamine was observed in all patients. The vital capacity increased an average of 19.8 per cent over the control volume. The subsequent administration of the isopropyl aerosol increased the vital capacity only to 20.0 per cent over the control value. To eleven patients epoxytropine tropate methylbromide was administered by intermittent positive pressure breathing on inspiration (IPPB/I) employing the Bennett valve, usually set at 15 to 18 cm of water pressure. In these patients the average increase in vital capacity was 13.8 per cent, which increased further to 20.8 per cent over the control value after subsequent administrations of Isuprel (Fig. 2). The average improvement with methyl bromide compares favorably with several adrenergic aerosols studied in a similar group of patients in our laboratory.

The maximal breathing capacity measurements showed an average increase of 29.3 per cent over the control value after Pamine aerosols in eleven patients. This, however, increased to 63.6 per cent over the control

value after subsequent Isuprel administration. In a second group of eleven patients, receiving both aerosols by IPPB/I, the average increase of the maximal breathing capacity after the methyl bromide aerosol was 12.3 per cent and this increased to 32.3 per cent over the control value after the isopropyl aerosols (Fig. 2).

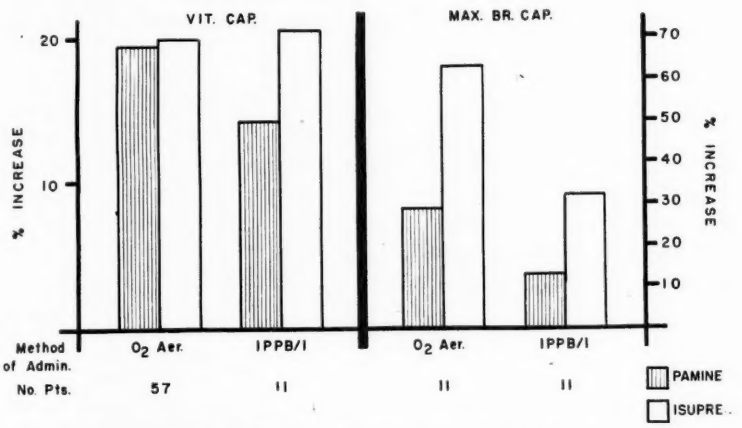

Fig. 2. Changes in the vital capacity and maximal breathing capacity in patients with chronic bronchial asthma after aerosols of Pamine followed by Isuprel aerosols, administered by the direct aerosol route and by intermittent positive pressure breathing on inspiration.

3. Clinical Studies.—Solutions of methylbromide for aerosol use in dosage of 0.33 mg per cc were given to a group of eighteen patients (six in each group) for clinical trial in home or hospital employing one of the following techniques: (a) hand bulb nebulization with the Vaponefrin nebulizer—employing two to six inhalations at intervals not more often than one hour apart; (b) continuous nebulization of 1.0 cc amounts (fifteen minutes' duration) employing the Eliot air pump unit* and Vaponefrin nebulizer—at four to six hour intervals as needed; and (c) continuous nebulization of 1.0 cc amounts (fifteen minutes' duration) employing the Bennett valve unit with oxygen for intermittent positive pressure breathing.[11] (IPPB/I).

These patients were all troubled with progressive bronchospastic disease due to either chronic bronchial asthma or chronic pulmonary emphysema. They had previous experience with the basic techniques described and had employed a wide variety of bronchodilator aerosol preparations. Good relief from bronchospasm of 1 to 3+ intensity was noted in the patients employing the techniques (b) and (c)—namely continuous aerosols using

*Eliot Medical Plastics Co., Washington Street, Lynn, Mass.

0.33 mg epoxytropine tropate methylbromide. The patients in group (a) using the hand bulb nebulizer technique reported adequate relief from mild attacks with two to six inhalations. They noted less relief when the attacks were moderate to severe. Under such circumstances they found Vaponefrin or the isopropyl aerosol more beneficial. There were three patients in this group with associated hypertension and labile vasomotor systems who tolerated poorly larger dosage of these adrenergic agents and preferred the methylbromide aerosol because of the absence of side effects.

Side Reactions.—The only side reaction noted during or following treatment was slight dryness of the oropharynx which was observed by several patients only after repeated administration of the drug employing 1 cc dosage of 0.33 mg. None of the patients experienced shakiness, palpitation, tachycardia, headache, mydriasis, nausea or vomiting. There were no significant changes noted in the pulse rates and blood pressure recordings taken on twenty-six patients before and after treatment.

CONCLUSIONS

1. A new synthetic anticholinergic agent, Pamine (Epoxytropine tropate methylbromide), administered as an aerosol, was found to be effective in relieving bronchospasm in patients with chronic bronchial asthma.

2. An aerosol solution containing 0.33 mg of the methyl bromide per cc demonstrated effective and prolonged protection against the bronchospastic effects of intravenous methacoline in patients with chronic bronchial asthma studied in the laboratory.

3. Subjective relief from bronchospasm was observed and correlated with the improvement in vital capacity in sixty-eight patients and the maximal breathing capacity in twenty-two patients. The greater the degree of bronchospasm, the greater was the improvement noted in vital capacity and maximal breathing capacity measurements.

4. An additional group of eighteen patients (six in each group) employed the bromide aerosols with one of these techniques: (a) hand bulb nebulization, two to six inhalations; (b) continuous aerosolization of 1.0 cc with air pump; and (c) continuous aerosolization of 1.0 cc with IPPB/I. The best clinical results were noted with the (b) and (c) techniques. Hand bulb nebulization was effective in the mild attacks and less effective than adrenergic bronchodilator aerosols in the moderate to severe attacks.

5. Undesirable effects were not observed following hand bulb nebulizations or continuous aerosol therapy with 0.33 mg per cc solution of methyl bromide. Several patients noted mild drying of the oropharynx after repeated continuous aerosol therapy. The absence of cardiovascular side

effects is an advantage in the use of this compound in patients with labile vasomotor systems, hypertension, tachycardia and cardiac disease.

6. The improvement in the more static vital capacity test was comparable to but less than observed after the use of an adrenergic bronchodilator aerosol. The improvement in the more dynamic maximal breathing capacity was not as significant. This would suggest routine clinical usefulness in overcoming the latent bronchospasm of the chronic asthmatic patient. The use of the adrenergic aerosols could then be employed for the frank attack not responsive to epoxytropine tropate methylbromide aerosols.

7. The possible combined usefulness of these aerosols with an adrenergic agent and their value in the relief of bronchospasm in patients refractory to adrenergic aerosols are being explored.

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TAINTER ELECTED PRESIDENT OF ACADEMY OF SCIENCE

Dr. M. L. Tainter, director of the Sterling-Winthrop Research Institute since 1946, has been elected president of the New York Academy of Science, the nation's fourth oldest scientific society, for a one-year term ending December 1955. Dr. Walter S. Root, professor of physiology, College of Physicians and Surgeons, Columbia University, was named president-elect.

RELATIONSHIP BETWEEN A CAREFUL DIETARY STUDY AND CORTISONE THERAPY IN THE TREATMENT OF INFANTILE ECZEMA

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Lynn, Massachusetts

THE HISTORY of the patient has assumed an increasingly important role in the last twenty years in the diagnosis and treatment of allergic conditions. It has to some extent superseded dermal testing. The cases outlined below re-emphasize the value of the history, especially a dietary history, if cortisone is to be used most effectively in infantile eczema.

It was early recognized that cortisone was effective in eczema, as the rash and itching cleared up quickly and usually completely within a few days of this therapy. Glaser,[2] Hill,[3] and others have reported such success in detail. However, it was soon noted that such relief was only temporary, in that it depended upon continuation of the cortisone therapy, since the eczema recurred promptly upon omission of this form of therapy. Lever[4] says "While the response to cortisone in eczema is good, on the other hand the rebound on discontinuation of the therapy is worse than in most diseases."

A situation similar to this is found in diabetes and in cretinism, where failure to continue treatment results in a relapse; however, the condition with regard to cortisone is different, owing to the not infrequent and serious side effects which may result. In this connection Forsham[1] mentions a formidable list, as follows: excessive weight gain, negative nitrogen balance, hypochloremic-hypokalemic alkalosis, glycosuria, acne, hirsutism, amenorrhea, pigmentation of the skin, striae of the skin, and insomnia. Such are the known possible side effects. It is too early in cortisone history to know what the remote effects may be.

Such side effects as have been listed, and presumably remote ill effects as yet unknown, increase in frequency and severity if cortisone therapy is extended over longer and longer periods. Many institutions now have had cases of eczema maintained on cortisone not only for months but for two years or more, certainly at considerable expense to someone and not without definite risk to the patient's immediate and future health. In view of this situation, any method of attaining successful alleviation of the eczema, and at the same time curtailment of the cortisone therapy, would seem to be more than welcome to the patient and to the physician. Such a method seems to be at hand. Although I have only two cases to report,

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From the Allergy Clinic of the Lynn Hospital, Lynn, Massachusetts.

Read in part at the Tenth Annual Congress of the American College of Allergists at Miami Beach, Florida, April 9, 1954.

the results seem so definite and so significant that I was impelled to report them even at the risk of seeming to be premature.*

The method is as follows. A careful detailed dietary history is essential. Every formula and change in formula, every new food added, and each food omitted from the diet must be noted. The relationship of these dietary changes must be related, if possible, to the onset and to any remissions or exacerbations in the eczema. In this way a tentative diagnosis as to the causative food factor can frequently be made. The history should also be used to determine any contactant which may have etiologic significance.

After having made a tentative diagnosis as to the food factor, the second step should be taken. This consists of initiating the cortisone therapy. Sufficient cortisone is given to clear up most, but not all, of the eczema. Some of the skin lesions are left. This remainder of the rash is to be used as an index as to whether or not the food factor has been correctly identified. If such is the case, exclusion of the suspected food from the diet should result in the disappearance of this last remaining eczematous lesion or at least in a definite improvement of the condition. Further confirmation of the diagnosis may be obtained by then resuming the suspected food in the diet and noting a return of the "index" lesion. Arriving at the point when a given food is incriminated, such food should be excluded absolutely from the diet. When the combination of cortisone and dietary exclusions have cleared the skin, the time is ripe to begin a gradual reduction of the cortisone dosage. I have reduced the cortisone 12½ mg every fourth or fifth day until none is given. The skin has remained clear meanwhile.

The next step is gradually to reintroduce the causative food into the diet. In the case which involved cereals, I returned the various cereals at intervals of a few days. In the case which involved milk, I returned the milk gradually, one ounce every few days. In neither of the cases to be detailed later did the eczema recur, although the cortisone was omitted after one month's treatment and the causative food factor was restored to the diet. Both infants are now on a general unrestricted diet; neither has received cortisone for several months, yet at no time has there been any recurrence of the eczema.

CASE REPORT

Case 1.—R. L., age two months, was first seen on October 2, 1953, at that time having a severe generalized eczema of two weeks' duration. A formula of evaporated milk and water had been used, and later a Dryco formula was undertaken without benefit to the skin. Corn cereal and apple sauce were also included in the diet. On October 7 cortisone therapy was started with a dosage of 25 mg four times daily. By October 13 the skin was improved, but by no means clear, on Dryco and 100 mg of cortisone. Goat's milk was substituted for Dryco. On October 21 the skin

*Since reading this paper at the meeting of the American College of Allergists on April 9, 1954, I have been able to duplicate the results in nine other cases.

was much improved with no moist areas and some scaling. Reduction of the cortisone by one-half tablet every fourth day was begun. By November 4 the child was receiving only 37½ mg daily, with no recurrence of the eczema. Banana, carrots, and spinach were added to the diet at four-day intervals. On November 18 the child had had no cortisone for a week, and the skin was clear and smooth. The formula at this time consisted of 9 ounces evaporated goat's milk and 16 ounces water. On December 17 the child's skin was clear, its weight 13 pounds, six ounces, height twenty-six inches, and potato and barley were added to the diet. Intradermal skin tests were negative for whole egg and cow's milk. Goat's milk was gradually replaced with cow's milk, one-half ounce at a time. By March 3, 1954, the formula contained 11 ounces of evaporated cow's milk and 14 ounces water. The skin has remained clear, and the environment had remained unchanged. On June 6 the skin was still clear.

Case 2.—B. K., age six weeks, was first seen on September 30, 1953, with generalized eczema. The rash had appeared ten days previous and four days after the introduction of a mixed cereal into the diet. Cortisone, 25 mg four times a day, was instituted, and all cereals were omitted. Drisdol and cevitamic acid were substituted for vifort. The formula consisted of 17 ounces milk, 8 ounces water and 3 tablespoons cartose, five ounces of this being given every four hours. By October 14 steady improvement in the skin had been noted, and reduction of the cortisone was begun at the rate of 12½ mg every fifth day. On October 23 the skin condition was still good, and banana and meat were added to the diet. The child's weight was nine pounds, fourteen ounces. Intradermal skin tests were negative for wheat, oats, rice, milk, and egg. The skin was still clear on November 5, and on November 19 the child had had no cortisone for five days. Rice was resumed in the diet. At this time the weight was ten pounds, four ounces, and the height twenty-two inches. The skin was still clear on December 10. By January 4, 1954, rice, oats, pablum and vifort had been resumed without recurrence of the eczema. The weight at this time was thirteen pounds, thirteen ounces, and the height twenty-five inches. The environment had been unchanged. The child was seen again on May 21 and June 6 and on both occasions the skin was clear.

SUMMARY

Cortisone therapy has been a most effective measure in eczema. It has, however, had two serious disadvantages. First, it has been only a palliative measure; second, prolonged treatment is not without the risk of forbidding side effects. While neither cortisone therapy nor dietary exclusion therapy has given satisfactory results, the combination of these methods in the cases outlined above leaves nothing to be desired.

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31 Broad Street

TREATMENT OF ALLERGIC RHINITIS OF POLLEN ORIGIN BY LOCAL APPLICATION OF A SUSPENSION OF CORTOGEN ACETATE WITH CHLOR-TRIMETON MALEATE

WILLIAM H. EVANS, M.D., F.A.C.A.
Youngstown, Ohio

SINCE THE topical administration of cortisone has been so widely used in many fields of medicine and it has been generally recognized, on the basis of many clinical and experimental observations, that it is efficacious in blocking the allergic inflammatory reaction, it is somewhat surprising that there have been so few reports of its use locally in the treatment of nasal inflammations of allergic origin. My associates and I began our clinical studies on this problem in 1949, when we received our first small supply of Cortogen.® Later, we experimented with the topical administration of Chlor-trimeton maleate,® and finally, with the combined suspension of Cortogen acetate with Chlor-trimeton maleate.* The results of these preliminary investigations have been reported previously.[2,3]

Our initial trials with Cortogen in the treatment of nasal conditions yielded somewhat equivocal and inconclusive results, partly because our supply of the material was limited and we used it very sparingly, and partly because we experimented with various dilutions and various methods of local application. Our experience with the topical administration of chlorprophenpyridamine maleate alone was favorable. Its action in shrinking the nasal tissues is obviously different from that of epinephrine, ephedrine or Neo-synephrine.® Besides its local vasoconstricting action, presumably Chlor-trimeton makes capillaries less permeable so that fluids do not gain access to the intracellular spaces so readily. The shrinking of the nasal mucosa by Chlor-trimeton apparently enhances the effect of Cortogen. Our experience has shown that the mixture of these two products is more effective in relieving inflammation of the nasal mucosa than is either agent alone. In all our more recent work, we have used the mixture of the two drugs in suspension.

The present report deals with a systematic study made during the spring and summer of 1953 on the effects of local nasal applications of the Cortogen-Chlor-trimeton suspension in a group of seventy-seven patients with allergic rhinitis caused by the pollens of grasses and ragweed. The

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Presented at Decennial Congress of the American College of Allergists, Miami Beach, Florida, April 10, 1954.

This report is an abridged version of that presented at the meeting of the American Society of Ophthalmologic and Otolaryngologic Allergy, October 16, 1953, Chicago, Illinois.[3]

*Brand of cortisone acetate with chlorprophenpyridamine maleate, supplied by the Schering Corporation, Bloomfield, New Jersey, courtesy of Dr. George Babcock. Each milliliter of suspension contains 5 milligrams of cortisone acetate, 2.5 milligrams 1-parachlorophenyl-1-(2-pyridyl)-3-dimethylaminopropane maleate, with Benzalkonium chloride U.S.P. 0.02 per cent added as preservative.

majority of the patients who received this treatment had been observed during previous "hay-fever" seasons. Most of them had been under our care for several years and had been subjected to skin sensitivity tests and had had repeated examinations for eosinophils in the nasal smear. Many of them had had various types of therapy, including hyposensitization procedures, antihistaminics and sublingual pollen tablets. Thus an opportunity was afforded for making a clinical evaluation on the basis of comparative results.

The technique used at present in the local administration of the suspension of the two products is as follows: In office treatments, a thin cotton pledget saturated with the Cortogen-Chlor-trimeton mixture is placed against the nasal septum and allowed to remain for a minimum of forty-five minutes. It is then placed against the lateral nasal wall and the patient is instructed to blow out the pack in another forty-five minutes. Since, in our experience, spraying the nose with the suspension has not been so effective as the use of the pack and drops, we instruct the patients as to how they should administer the drops at home. They are told to lie on the bed or couch with the head hanging over the side and to instil three or four drops of the suspension in each nostril. They are to remain in this position for two or three minutes and are told not to blow the nose. If any of the suspension trickles down into the throat, it is to be swallowed, and if any runs out of the nose, it is to be wiped away.

In this series of seventy-seven cases, the medication has been administered as drops or as packs, or both, and in some instances only a few applications were given. We advise the patients to discontinue the applications as soon as relief is obtained, or at the termination of the season of the specific pollen to which the patient is sensitive. The usual prescription was to use the drops every three hours, or oftener, if necessary. During the season when the pollen count was extremely high, some patients found it necessary to use the suspension every hour or two. As the pollen count decreased, many were comfortable if they used the drops only two or three times a day.

It must be remembered that this group of people represented private patients who came to our office for relief, and it was our responsibility to see that they received as prompt and complete relief as possible. Consequently, for those patients who did not receive satisfactory symptomatic results, some additional treatment in the form of antihistaminic drugs by mouth or other measures was employed. In a few instances, the patients objected to the trouble connected with placing the drops in the nose and preferred to depend entirely on antihistaminic agents that they could take by mouth.

In many instances, the local administration of both these products gave more prompt and lasting relief than anything previously used. In forty-four cases, the suspension, administered as packs and drops, was the only treatment, and the results were satisfactory. In twenty-five cases,

TABLE I. SUMMARY OF CASES TREATED DURING GRASS-POLLEN SEASON

Patients	23
Youngest	9
Oldest	62
Male	10
Female	13
Cortogen-Chlor-trimeton suspension alone	15
Excellent	9
Good	3
Fair	1
Poor	2
Suspension plus antihistaminic by mouth	5
Excellent	2
Good	3
Suspension plus hyposensitization and/or other therapy.	3
Good	2
Poor	1
Drops irritating to nasal mucosa	3

TABLE II. SUMMARY OF CASES TREATED DURING RAGWEED-POLLEN SEASON

Patients	36
Youngest	3
Oldest	59
Male	25
Female	11
Cortogen-Chlor-trimeton suspension alone	23
Excellent	8
Good	10
Fair	3
Poor	2
Suspension plus antihistaminic by mouth	13
Excellent	3
Good	7
Fair	2
Poor	1
Suspension plus hyposensitization and/or other therapy.	0
Drops irritating to nasal mucosa	3

TABLE III. SUMMARY OF CASES TREATED DURING GRASS-POLLEN AND RAGWEED-POLLEN SEASONS

Patients	18
Youngest	6
Oldest	49
Male	10
Female	8
Cortogen-Chlor-trimeton suspension alone	6
Excellent	2
Good	4
Suspension plus antihistaminic by mouth	7
Excellent	2
Good	2
Fair	1
Poor	2
Suspension plus hyposensitization and/or other therapy.	5
Excellent	1
Good	3
Fair	1
Drops irritating to nasal mucosa	3

Chlor-trimeton or other antihistaminic tablets were also taken by mouth. In a few instances, when the patient was extremely hypersensitive, injections of the offending allergen and/or house dust were continued during the season of specific sensitivity, along with the local treatment with the combined suspension.

The essential data regarding the cases in this series are shown in Tables I, II, and III, which summarize the results in twenty-three patients treated for grass-pollen allergy, thirty-six patients for ragweed-pollen allergy and eighteen patients treated for both grass-pollen and ragweed-pollen allergy. As these tables demonstrate, the results were good or excellent in the majority of instances, either with the local application of Cortogen-Chlor-trimeton suspension alone, or in combination with Chlor-trimeton or some other antihistaminic drug by mouth. In five instances, the results of treatment were unsatisfactory, even though the drops were given a fair trial. In three other instances, the patients complained that the drops caused a burning sensation of sufficient severity that they did not wish to continue using them. Six other patients also complained of the burning sensation, but continued treatment because of the satisfactory relief of symptoms. This sensation is due to the Chlor-trimeton or the Zephiran® (1:5000) used as a preservative, and not to the Cortogen. We have observed no evidence of any damage to the nasal tissues, even with prolonged administration of the suspension, and there have been no untoward reactions attributable to the Cortogen. None of the patients complained of drowsiness or other general reaction from the antihistaminic action of Chlor-trimeton. Repeated eosinophil counts during the course of treatment indicated that the eosinophil count in the nasal smear does not parallel exactly the degree of clinical improvement, a fact that has also been noted by Dill and Bolstad[1] in a series of cases in which they used a cortisone preparation locally in the nose. In some instances in our series, there was a concomitant reduction in the eosinophil count, and in others, the eosinophil count remained fairly high or fluctuated considerably during the course of treatment.

It should be noted also, in evaluating the results of treatment with the combined suspension in this group of patients that this was a particularly "bad" season for hay fever in the Youngstown area, and the pollen counts were the highest ever recorded. A count of 793 grains per cubic yard of air during a twenty-four hour period was registered this season; the previous high count was recorded in 1944, when the peak reached a count of 600.[4]

Despite these high pollen counts, the results with the local application of the Cortogen-Chlor-trimeton suspension were most encouraging and some patients were afforded practically complete relief. Among the patients treated during the grass-pollen season with the Cortogen-Chlor-trimeton suspension alone, nine had excellent results; three, good; one, fair, and two had unsatisfactory relief. Five patients in this group of twenty-

three patients also received Chlor-trimeton or other antihistaminic agent by mouth, with excellent results in two cases and good results in three. Three patients had additional hyposensitization procedures or other therapy, with good results in two and poor effects in one instance.

Twenty-three of the thirty-six patients treated for ragweed-pollen allergy received only the local applications of the combined product suspension. Results were excellent or good in eighteeen, fair in three and poor in two. In thirteen cases in this group, additional antihistaminics were given by mouth, with results good or excellent in ten, fair in two and poor in one.

Eighteen patients received treatment with the Cortogen-Chlor-trimeton suspension throughout both the grass and ragweed seasons. This was sufficient to produce good or excellent results in six. Seven patients had antihistaminic tablets by mouth, during at least part of the treatment period, and the results were satisfactory in four, fair in one, and poor in two. Other therapeutic measures were added in five cases, with satisfactory results in four, and fair results in one.

After many years' experience in the treatment of nasal allergy, it is my clinical impression that the patients with grass-pollen and ragweed-pollen hypersensitivity have been kept more comfortable during this past season of high pollen counts than they were in other years when other types of treatment were employed. This does not imply that the combined suspension of the two products discussed constitutes a definite answer to the problem of nasal allergy; but it does offer a new means of affording satisfactory or considerable relief from the distressing symptoms. Our experience justifies a recommendation for its continued and more widespread use by the medical profession.

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510-517 Dollar Bank Bldg.

AMERICAN GERIATRICS SOCIETY

The 1955 annual meeting of the American Geriatrics Society will be held at the Hotel Roosevelt in New York on Thursday and Friday, April 21-22, 1955. The program will include panels on cancer, cardiac and circulatory diseases, osteoporosis, and diabetes in the aged.

OBSERVATIONS OF THE CLINICAL TRIAL OF TROPIN-4-CHLOROBENZHYDRYL ETHER HYDROCHLORIDE

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Section 1. Observations by Dr. Lawrence Halpin

This report describes our experiences with a new antihistaminic compound (Tropin-4-chlorobenzhydryl ether hydrochloride), designated FC-1 by the manufacturer.* Preliminary experimental work will not be repeated here, as this has been adequately presented by Kaplan, Aaronson and Ehrlich[1] in studies parallel to ours.

FC-1 was administered to eighty-one selected patients seen in private practice from July through October, 1953, an "average" season as judged by pollen counts. Selection of this study group was based upon a clinical indication for antihistaminic drug, with no regard for age, sex, nature of complaint, nor other contributing factors.

The drug was supplied to us as a white, scored tablet in a dose of 5 mg, and it had been suggested that the optimum dose might be one tablet daily, with variations as required to meet individual needs. Investigative studies were completed to a degree compatible with the patient's symptoms and findings. Clinical diagnoses were recorded as follows: fifty-four patients had uncomplicated seasonal hay fever with active complaints at the time of drug administration; sixteen individuals presented symptoms of seasonal hay fever and seasonal bronchial asthma; perennial allergic rhinitis was the diagnosis in seven instances; chronic urticaria was the source of distress to three patients, and in one person chronic itching of the hands due to a persistent hand dermatitis suggested oral antihistaminic therapy. Insufficient follow-up reports necessitated the exclusion of three records from the reported results.

FC-1 was withheld from these patients until symptoms were present. The initial dosage was one tablet (5 mg) daily, with this being used-either in the morning or evening depending upon the patient's desires and symptom-peaks, and subsequent adjustments were made to meet individual necessities. All patients were seen twice weekly with superficial examinations and thorough questioning being a part of the office routine, and laboratory work, consisting of red and white blood counts, hemoglobin determinations and differential counts, was also done at bi-weekly intervals during the course of study. No appreciable changes were noted in the blood pictures during the period of drug administration.

*Drug supplied and study supported in part by a grant from the Schenley Corporation.

Drowsiness, dizziness and excessive dryness of mucous membranes were not markedly present with this preparation. This was attributed to the level at which the dosage was maintained.

FC-1 was discontinued on two patients because of inadequate and unsatisfactory clinical response. Previous experience with other antihistaminic agents in these individuals had shown similar lack of relief. Early in the program, marked drowsiness, dryness of the mouth, nausea and vague arthralgia forced one patient to refuse further therapy with this preparation. These distressing complaints had persisted regardless of the dosage or the interval. Because the original dose had been one tablet (5 mg) daily and because these complications appeared in one of the first patients studied, subsequent individual doses were decreased by 50 per cent in all patients. Symptoms were well controlled on 2.5 mg once or twice daily. On this schedule, the incidence of side effects was remarkably low in comparison with Kaplan's[1] over-all reaction figure of 23 per cent. Though the dosage was fluctuant, the optimum amount for most patients was found to be 2.5 mg twice daily, but twelve adult patients were comfortable on 2.5 mg daily. Prolonged relief (eight to twelve hours) was noted by several patients, and good response was observed by twenty-four individuals for as long as twelve to twenty-four hours.

This preparation provided relief of equal degree to that noted with other antihistaminic drugs. In no instance were asthmatic symptoms appreciably relieved nor reduced in severity with FC-1. Similar findings have been our experience with other drugs of this nature. The majority of the patients studied had been on other antihistamines in the past. Thirty-nine of this group were treated specifically with pollen, mold or dust extracts in association with antihistaminic therapy. Of the eighty-one patients, forty-two received no medication other than FC-1, except when aminophyllin or similar drugs were prescribed for the relief of asthmatic symptoms.

In general, the clinical response with FC-1 compared very favorably with other well known and often used antihistaminic agents. Statements by patients in this study varied from "the most relief" to "indistinguishable from other drugs that have been used." As some of our patients were children, little reliability can be placed in their statement of results. Twenty patients were given the drug for three days, then no medication for three days, with a return to FC-1 dosage. It was felt that this interruption of therapy might give us a better indication of drug efficacy. Definite amelioration of symptoms was noted on "drug days." FC-1 appeared to possess the following advantages: Infrequent administration, prolonged satisfactory relief, and relatively few serious side-effects on a low dosage program.

SUMMARY

A new antihistaminic drug, FC-1, was given to eighty-one patients during the mold and ragweed seasons of 1953 with encouraging results.

Antihistaminic action was observed to be satisfactory and prolonged. In only one instance were there side-effects of a degree necessitating cessation of therapy.

CONCLUSION

It is our impression that this new type of antihistaminic drug has a place in the therapeutic regime of the physician.

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Section 2. Observations by Dr. L. O. Dutton

A representative group of forty-nine allergy patients, presenting chiefly seasonal hayfever with or without asthma and a few miscellaneous symptoms, was studied and treated with the new antihistamine FC-1. These are grouped and selected to represent adults with seasonal hayfever, adults with seasonal hayfever and asthma, children under twelve years of age with seasonal hayfever, and children twelve years of age and under with seasonal hay fever and asthma. There are also a group of adults and children with miscellaneous allergy problems. These cases have all been followed with complete blood counts done immediately before treatment started and at intervals during the course of treatment.

The dose administered was in most cases 2.5 mg daily taken in the early morning. A few patients were given this dose twice daily, a few were given 1.25 mg and at least one patient received .625 mg.

We attempted to distribute these cases between simple allergy problems of a routine nature and to include a number of rather persistent difficult problems which have failed to respond satisfactorily to other treatment. No placebal controls were used as I preferred to gauge the effectiveness of this drug by other means which I considered more reliable.

In the over-all analysis, the results have been recorded as "good," "satisfactory" and "failure," "satisfactory" being represented to mean that the drug has been of sufficient value to be a therapeutic help. The results in the over-all cases have been good in thirty cases (60 per cent); satisfactory in eleven cases (22.5 per cent); failure in eight cases (17 per cent). Side effects were present in fifteen cases (30 per cent), and side effects were sufficiently severe to discontinue the drug in four cases (8 per cent).

Adults with seasonal hayfever showed good results in eight cases, satisfactory results in one case, and failure in two cases. Side effects were present in four cases.

Among adults whose diagnosis was seasonal hayfever with complicating asthma, the results were as follows: good eleven cases, satisfactory one case, failure two cases. Side effects were present in five cases.

Of those children under twelve years of age suffering from seasonal hayfever, the results were good in four cases, satisfactory in one case, with no failure. No side effects were present.

Of the children twelve years of age and under with seasonal hayfever and complicating asthma, the results were good in all four cases, and no side effects occurred in this group.

Adults with miscellaneous allergic conditions showed good results in four cases, satisfactory results in five cases, and failure in three cases. Side effects were present in six cases. In this miscellaneous group the cases included a variety of allergic symptoms and all presented difficult treatment problems.

In children with miscellaneous conditions, results were recorded as satisfactory in three cases with failure in one case. Side effects were present in none of these cases. These cases were likewise difficult treatment problems.

Our final impression concerning these various groups is that in each of them, the drug is well worth while and in many of these cases, as indicated by the details of the individual reports, the drug has been more satisfactory to the patient than other antihistaminics previously tried. The reverse of this has also been true in some of the failure cases. Noteworthy has been the observation that a few cases which have consistently failed to respond to other type of therapy and other antihistaminics, have obtained an appreciable degree of relief from the use of this drug. There have also been a few cases in which the drug was tried in otherwise untreated hayfever with complete control of the symptoms.

Another significant fact observed is the more uniform "good" and "satisfactory" results obtained among children twelve years of age and under and the complete absence of side effects in this age group is notable. It has also been observed among this age group that the adult dose (2.5 mg) has been tolerated well.

Among the adults with side effects it should be emphasized that many of the cases were individuals with rather widespread drug intolerances, and although the failure percentage is high for this category it is felt that the group selected would in all probability show a high side effect percentage following the use of any drug. The side effects in the order of their frequency were: drowsiness (noted nine times), dizziness (four times), nausea (twice), vomiting (twice), inco-ordination, blurring of vision, weakness, and headache (noted once each). Most of these were minimal and only four cases chose to discontinue the drug because of side effects.

Without being burdensome concerning the hematological findings, it was our impression in a study of 125 blood counts done on these patients that there was no significant effect upon any of the formed elements of the blood.

In addition to these forty-nine cases, about fifty other cases have been

SUMMARY

Diagnosis	Results			Side Effects		
	Good	Satisfactory	Failure	None	Present	Characterized By:
Over-all cases	30 (60%)	11 (22.5%)	8 (17%)	34 (70%)	15 (30%) Sufficient to discontinue in 4 (8%)	Drowsiness in 9 cases; incoordination 1; dizziness 4; blurring of vision 1; weakness 1; headache 1; nausea 2; and vomiting 2.
Seasonal hay fever (adults)	8	1	2	7	4	
Seasonal hay fever (children 12 years of age and under)	4	1	0	5	0	
Seasonal hay fever and asthma (adults)	11	1	2	9	5	
Seasonal hay fever and asthma (children 12 years of age and under)	4	0	0	4	0	
Miscellaneous (adults) (Perennial asthma 7; urticaria 2; post-nasal drainage and abdominal pain 1; headache, precordial and abdominal pain 1; intractable cough 1)	4	5	3	5	6	
Miscellaneous (children under 12) (Perennial hay fever 3; nasal polyposis 1).	0	3	1	4	0	

given this drug with less careful scrutiny and without blood counts being taken. It is our final impression from these cases that the results have been essentially the same as outlined in the analyzed cases.

The general clinical impression is that the drug is a valuable addition to the battery of antihistaminics, that in some cases surpasses all others in effectiveness, and that it is particularly well tolerated by children.

We also get the general impression that the dosage may profitably be reduced to eliminate side effects. Perhaps a combination of this drug with some other suitable one may increase its effectiveness and decrease its side effects.

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FIFTIETH ANNIVERSARY MEETING—AMERICAN TRUDEAU SOCIETY

The American Trudeau Society, medical section of the National Tuberculosis Association, will hold its fiftieth anniversary meeting beginning May 23 at the Milwaukee Auditorium in Milwaukee, Wisconsin. The session, which is being held in conjunction with the annual meeting of the National Tuberculosis Association, will consist of three days of scientific papers, panel discussions, and special lectures on pulmonary diseases.

THE USE OF HYDROCORTISONE SUSPENSION IN NASAL ALLERGIC AND INFECTIOUS CONDITIONS

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CONDITIONS OF an inflammatory nature which cause partial or complete blocking of the nasal passages usually affect adjacent membraneous structures as well. This is especially true when an allergy is the causative factor. The sufferer faces long periods of annoyance and extreme discomfort either of a seasonal or perennial nature. His activities are impeded to a greater or lesser degree, even though systemic illness is a corollary in comparatively few instances. The treatment routinely employed for these conditions, while usually affording temporary relief, is not only inadequate but may leave the patient with secondary engorgement and blockage of the nasal passages and a dry, burning sensation in the nose and throat.

Having observed that hydrocortisone administered orally proved markedly beneficial to sufferers with allergic disorders, it occurred to the writer that the same agent applied topically would be even more effective because of the obvious advantages of applying the drug directly to the involved tissues.

Since symptoms in allergic rhinitis vary in degree of involvement, a comparatively small series of cases reported (Table I) serves to show the sort of alleviation attained when routine therapeutic measures are administered, compared to the dramatic results when the same persons received topical applications of hydrocortisone suspension. The fact that this drug was given to patients whose reactions to the administration of routine therapy for varying periods had been noted previously supplied the most convincing type of control possible. It showed the effect of two different kinds of therapy on the same person (spaced to obviate interference) rather than the effects of two kinds of therapy on different individuals.

METHOD AND RESULTS

Allergic Rhinitis.—The symptoms accompanying allergic rhinitis form a characteristic pattern. The mucous membranes of the nose and throat are pale, soft and thickened in appearance. The discharge from these tissues may be intermittent or constant, and may range from watery fluid to thick mucopus if a superimposed infection exists. In many instances, the discharging fluid runs down the posterior pharyngeal wall causing a reflex, paroxysmal cough. The discharge may act as a direct or reflex irritant of the bronchi and precipitate an attack of asthma. Complete blocking of the nasal passages, in some instances with polypi, may last for

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TABLE I. ALLERGIC RHINITIS

Case No.	Patient	Sex	Years of Age	Allergic Manifestations			Routine Therapy			Administration of Hydrocortisone Suspension	
				Reaction to	Symptoms	Duration of Symptoms	Agent Used	Period	Results	Period	Results
1	E.K.	M	24	Dust Ragweed Feathers	Clogged nasal passages. Sneezing. Cough. Wheezing. Mucopus on mucous membranes of nose and pharynx.	5 years	Hyposensitization with: dust, ragweed, feathers. Oral antihistamines. Nasal preparation.	2 yrs.	Fair	2 days	Nasal passages clear. Mucous membranes of nose and pharynx normal in appearance and free of mucus. Coughing, wheezing, sneezing stopped.
2	D.F.	F	39	Dust Timothy Feathers Molds	Perennial sneezing. Clogged nasal passages. Cough, worse at night. Headaches. Rhinorrhea.	1 year	Hyposensitization with: dust, autogenous and stock; timothy; molds; feathers. Oral antihistamines. Ephedrine and other nasal preparations.	6 mos.	Fair. Temporary relief.	2 days	Nasal passages clear. Coughing, sneezing stopped.
3	S.S.	M	35	Dust Mixed grasses Ragweed	Perennial sneezing. Pruritus of eyelids. Lacrimation. Clogged nasal passages. Rhinorrhea.	5 years	Hyposensitization with: dust, mixed grasses, ragweed. Oral antihistamines. Nasal preparations.	3 yrs.	Good	3 mos.	Mucous membranes normal in appearance after three days. Sneezing, rhinorrhea stopped. Disappearance of polypi after three months of continuous use.
4	L.K.	F	58	Dust	Perennial sneezing. Clogged nasal passages. Rhinorrhea.	2 years	Hyposensitization with: dust. Oral antihistamines. Nasal preparations.	over 3 yrs.	Fair	2½ days	Nasal passages clear. Sneezing, rhinorrhea stopped.
5	B.S.	M	36	Dust Trees Ragweed	Perennial sneezing, worse during ragweed season. Clogged nasal passages. Cough. Lacrimation.	1 year	Hyposensitization with: dust, trees, ragweed. Oral antihistamines. Nasal vasoconstrictor.	over 3 yrs.	Fair	2 days	Nasal passages clear. Cough, lacrimation stopped.
6	B.B.	F	29	Dust Molds	Perennial sneezing. Clogged nasal passages. Cough. Rhinorrhea. Upper respiratory infections frequent.	3 years	Hyposensitization with: dust, molds. Oral antihistamines. Cough preparations.	over 1 yr.	Good	2 days	Cough stopped. Mucous membranes much improved.
7	V.S.	F	16	Dust Feathers	Clogged nasal passages. Cough. Sneezing. Enlarged tonsils.	7 months	Hyposensitization with: dust, feathers. Oral antihistamines. Cough preparation.	8 mo.	Fair	2 days	Nasal passages clear. Cough, sneezing stopped. Mucous membranes appeared normal.
8	J.A.	M	12	Dust Wool Ragweed	Clogged nasal passages. Sneezing. Rhinorrhea. Lacrimation.	2 years	Hyposensitization with: dust, wool, ragweed. Oral antihistamines. Nasal preparations.	1½ yrs.	Fair	2 days	Nasal passages clear. Sneezing, rhinorrhea stopped. Only a trace of mucoid nasal secretion.

extended periods, and bouts of sneezing are frequent. While the nasal passages are primary sites of involvement, the sufferers may be subject to impairment of the senses of taste and smell, congested conjunctivae, swollen eyelids, and copious lacrimation.

While treating these patients, after skin tests have indicated the kind of hyposensitization required, roentgenographic studies of the head and chest are routine procedure for the purpose of visualizing the inner structures and of ruling out abnormalities not attributable to the allergy. Previous regimes included prescriptions for nasal drops containing an antihistamine, an antibiotic and a vasoconstrictor. Cough mixtures usually contained codeine or dihydrocodeinone. In addition, antihistamines were given orally. The period of relief afforded by these measures is brief at best, and constant repetition of their use has a distinctly deleterious effect on the mucous membranes of the nose and throat.

In preparing hydrocortisone for application to the nasal passages as drops, 20 milligrams of the drug are used per cubic centimeter of normal saline solution. Hydrocortisone is not soluble but remains in suspension; the mixture must be well shaken before use.

To administer the drug, the patient lies on his back on a table or couch so that his head may be tilted back over the end. The hydrocortisone suspension is placed in each nostril, and the patient remains in the supine position for a minute or two so that the liquid may spread over the nasal membranes. Three to five drops are instilled in each nostril three times daily.

The response of the tissues to this topical application of hydrocortisone suspension was most remarkable, changing the entire picture. The discharge which had aggravated all other symptoms had subsided, the swelling gave way to clear air passages in the nose, and nasal and pharyngeal membranes were very nearly normal in appearance. Without the postnasal drip, the coughing ceased. Untoward reactions from the use of the drug were not encountered even though, as in the case of S. S., it was used continuously for three months. The other patients who had received treatment for several days only, remained symptom free for periods ranging from four to sixteen days.

To augment Table I, case histories of three patients are given in detail. It is believed that these examples are typical.

CASE REPORTS

Case 1.—E. K., a man twenty-four years of age, whose symptoms extended back over a period of five years, and which were especially severe during August and September, had a cough accompanied by wheezing which resulted from a superimposed infection. He had been treating himself with different diets, antihistamines, cough medicines and vitamins with very little improvement.

Physical examination showed the man to be in a generally debilitated state. The mucous membranes of the nose were pale and swollen and, together with the pharynx, were covered by mucoid exudate. The lungs emitted an occasional wheeze on deep

TABLE II. INFECTIOUS RHINITIS

Case No.	Patient	Sex	Years of Age	Symptoms	Duration of Symptoms	Routine Therapy			Administration of Hydrocortisone Suspension	
						Agent Used	Period	Results	Period	Results
1	H.D.	M	10	Temperature 101 degrees F. for one day. Clogged nasal passages. Mucopurulent discharge. Cough.	2 weeks	(1) Terramycin. (2) Ephedrine nasal preparation. Cough mixture.	(1) 48 hrs. (2) 10 days	Temporary relief.	2 days	Nasal fossae:— Color good: air passages clear. Pharynx:— Membranes improved: no discharge Cough stopped.
2	M.A.	F	20	Clogged nasal passages. Mucopurulent discharge. Cough.	5 days	Nasal vasoconstrictor with antibiotic. Cough mixture.	8 days	Temporary relief.	2 days	Nasal fossae:— Color good: air passages clear. Pharynx:— Membranes less inflamed. No discharge. Cough stopped.
3	E.S.	F	14	Temperature 100.2 degrees F. for two days. Clogged nasal passages. Mucopurulent discharge. Cough.	3 weeks	(1) Penicillin. (2) Nasal preparation. Cough mixture.	(1) 2 days (2) 11 days	Temporary relief.	2 days	Nasal fossae:— Edema subsided: very slight discharge Pharynx:— Slightly inflamed membranes. No discharge. Cough stopped.
4	L.A.	M	11	Clogged nasal passages. Mucopurulent discharge. Cough.	1 week	Nasal vasoconstrictor with antibiotic. Cough mixture.	7 days	Temporary relief.	2 days	Nasal fossae:— Color good: air passages clear. Pharynx:— Membranes improved. No discharge. Cough stopped.
5	S.W.	F	25	Clogged nasal passages. Mucopurulent discharge. Cough.	1 week	Nasal vasoconstrictor with antibiotic. Cough mixture.	7 days	Temporary relief.	2 days	Nasal fossae:— Color good: air passages clear. Pharynx:— Membranes clear of discharge. Cough stopped.
6	M.S.	M	36	Clogged nasal passages. Mucopurulent discharge. Cough.	9 days	Nasal preparation with antibiotic. Cough mixture.	7 days	Temporary relief.	2 days	Nasal fossae:— Color good: edema subsided. Pharynx:— Membranes improved. No discharge. Cough stopped.
7	L.R.	M	40	Clogged nasal passages. Mucopurulent discharge. Cough.	12 days	Nasal preparation with ephedrine. Cough mixture.	9 days	Temporary relief.	2 days	Nasal fossae:— Edema subsided. Very slight discharge. Pharynx:— Slightly inflamed membrane. No discharge. Cough stopped.
8	M.K.	F	38	Temperature 102 degrees F. for 36 hours. Clogged nasal passages. Mucopurulent discharge. Cough.	2 weeks	(1) Aureomycin. (2) Nasal preparation. Cough mixture.	(1) 48 hrs. (2) 10 days	Temporary relief.	2 days	Nasal fossae:— Edema subsided. Very slight discharge. Pharynx:— Slightly inflamed membrane. No discharge. Cough stopped.

expiration; otherwise, the examination was negative. Roentgenograms of the sinuses were hazy and showed thickening of the lining membranes. Films of the chest revealed no abnormalities. Skin tests showed moderate to marked reactions to dust, ragweed and feathers.

The patient was placed on a diet high in calories and proteins. Appropriate hyposensitization injections were given, with improvement noted after five months. Especially during the ragweed season, antihistamines were administered orally as well as vasoconstrictor nose drops because of the persistent hay fever symptoms. Temporary relief was obtained, but the frequent applicant of the drugs produced a dry, burning sensation in the mucous membranes of the nose and throat.

In March 1954 the patient contracted an upper respiratory infection. Mucous membranes of the nose and pharynx were edematous, inflamed and covered with mucopus. Wheezing was noted at the end of each respiration. There was a dry, hacking, ineffective cough, and a temperature 101 degrees. Terramycin® and a cough mixture containing ephedrine were prescribed with slight relief. The cough was due to a postnasal discharge which the Terramycin failed to control. At the same time administration of a nasal preparation containing an antihistamine, an antibiotic and a vasoconstrictor was used, but the condition remained substantially the same with only temporary alleviation.

Hydrocortisone suspension was administered as nose drops. After two days the nasal passages were clear, and the mucous membranes of the nose and pharynx were free of mucopus and had assumed an almost normal appearance. Both coughing and wheezing had subsided.

Case 2.—D. F., a thirty-nine-year-old woman suffered with alternate bouts of sneezing and blocking of the nasal passages for a year. The symptoms were more severe during the night. Physical examination showed the patient to be in a normal state of health. Other than that, the mucous membranes of the nasal passages exhibited the usual signs of allergic rhinitis; they were thickened and covered by mucus. The pharyngeal mucous membrane was pale and coated by mucus. No other abnormalities were noted. Roentgenograms of the sinuses showed thickening of the mucous membranes. The lungs were without abnormality. According to skin tests, there were varying degrees of sensitivity to dust, timothy, feathers, and molds.

Hyposensitization injections of autogenous dust, stock dust, feathers, timothy and molds were used with moderately favorable results. Further relief obtained from the use of antihistamines, ephedrine and other nose drops was brief. Hydrocortisone suspension was prescribed for use in the nose, and after two days the nasal passages were free of obstruction and the mucoid discharge had stopped.

Case 3.—S. S., a man thirty-five years of age, presented a history of lacrimation, pruritus of the eyelids, perennial sneezing, clogged nasal passages, and rhinorrhea of three years' duration. His brother suffers from pollinosis to ragweed, and his brother's son had infantile eczema. Examination showed the mucous membranes of the nose and pharynx to be pale and swollen; mucoid secretion was profuse. Each nasal fossa was almost filled by a polyp. Roentgenograms of the head revealed that the sinuses appeared hazy with thickening of their mucous membranes. As shown by skin tests, dust, mixed grasses and ragweed were the offending agents. For a long period, the patient had been using antihistamines orally along with a vasoconstrictor as nose drops. Temporary relief was obtained, but the man suffered with the usual effects of the drying of the mucous membranes of the nose and pharynx.

Hydrocortisone suspension was applied to the nasal passages. After three days, the eye symptoms had subsided, the mucoid secretions had stopped, and the mucous membranes presented a normal appearance. The use of the drug was continued for three months and by the end of that period the polypi had completely disappeared. The patient felt no untoward reaction from the use of the drug.

Infectious Rhinitis.—Although the same structures are involved in both allergic and infectious rhinitis, in the latter the symptoms and signs are intensified. The mucous membranes of the nose appear markedly congested, with the surfaces red, sufficiently swollen to block completely the air passages, and are covered with a profuse mucopurulent discharge. The mucous membranes of the pharynx are congested also; they appear inflamed and raw, and are covered by mucopus. This pharyngeal exudate together with the nasal fluid that discharges into the throat creates a severe hacking, choking and, at times, productive cough which is painful to the intensely inflamed or irritated tissues of the throat. Antitussives afford these patients very little relief, and are inclined to aggravate the existing groggy, tired feeling, loss of appetite and disturbed bowel action.

Since hydrocortisone suspension is known to be markedly superior to cortisone in combating inflammatory conditions, it was decided to use it topically in cases of infectious rhinitis (Table II). The form of administration and dosage that had produced such excellent results with allergic rhinitis were employed. The results were even more surprising, since the initial symptoms had the added factor of congestion. Fever, when present, was brought under control by an antibiotic.

Results from the amount of hydrocortisone suspension that has been used by the writer have proven so satisfactory that no attempt has been made to vary the dosage. For the same reason, adding an antibiotic to the drug in treating infectious rhinitis, or an antihistamine when treating allergic rhinitis, has not been deemed necessary.

SUMMARY AND CONCLUSIONS

The results obtained by the use of hydrocortisone suspension in cases of allergic and infectious rhinitis have been highly satisfactory.

The effect of the drug in controlling the postnasal discharge and cough was remarkable in both allergic and infectious rhinitis.

Asthma attacks accompanying allergic rhinitis were reduced in frequency and severity.

No tolerance to hydrocortisone suspension after continuous use was noted, nor were there any untoward side reactions.

It is believed that the topical use of hydrocortisone suspension is a valuable therapeutic agent in addition to the other measures used in the routine treatment of allergic and infectious rhinitis.

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EUPHORBIA PILULIFERA IN ASTHMA

(Historical Document)

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In connection with the use of euphorbia pilulifera for asthma, I have had the following interesting and instructive experience. I will go somewhat into details with the hope that they may prove of value to the profession.

In the spring of 1888, I was called to attend a man, fifty-five years old. The patient was a man of means and occupied a position of great trust and responsibility. He was suffering from a severe attack of asthma, brought on in this instance apparently by indiscretion in eating, as it was attended by a severe attack of indigestion. When I saw him he was sitting up in bed, breathing with difficulty, with whistling expiration which could be heard all over the room. He stated that he was subject to such attacks, probably four or five times a year. This one had come on at Atlantic City, a few days previous to my visit, and the physician who was called had given him a hypodermic injection of morphine, which had been followed by such severe vomiting that the patient begged me not to repeat it except as a last resort. I then gave him a mixture containing fluid extract of euphorbia pilulifera, potassium iodide, potassium bromide, and tincture of belladonna. I also ordered three drops of amyl nitrate to be taken by inhalation, and that half an ounce of glycerine should be given by injection, as his bowels were very much constipated. I saw him again the following day, and found that he had refused the mixture, after two doses, on account of the intensely disagreeable taste; so that later in the day, I found it necessary to give him a hypodermic of morphine gr. ¼, and atropine gr. 1-60. This was followed by the happiest results, the patient dropping into a quiet sleep in about ten minutes.

After this, I explained to him the importance of treatment in the periods between the attacks, ordering him a laxative pill and a stomachic, and telling him to pay special attention to diet and hygiene; and also advised him to spend the following August, when he was liable to an attack, in the mountains.

Although from time to time seeing other members of his family professionally, I saw nothing of this patient for some months, but heard indirectly that he desired to see me, as he had been cured of the asthma by the "Buffalo Asthmatic Institute," to which he had been sent by a friend. Finally, about Christmas, I met him, and he at once told me that he had only been waiting a few months to see if his cure held out to tell me about

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the treatment, and that he now felt he could reasonably feel cured, and that a number of his friends had also been treated with wonderful success in the meanwhile. He cited the case of a cousin who had been unable to lie down for years, but who was now able to sleep in the normal position.

I then went home with him, and he showed me the following drugs: The box he had received contained a box of pills, a box of capsules, and three bottles, also a couple of pamphlets with directions. The pills were to keep the bowels regular; the capsules contained quinine (gr. ii) to be taken when catching cold. One of the bottles contained a stomachic to be taken before meals for the avowed purpose of keeping the stomach in good condition; one of the other bottles held the "Asthma Cure," and was to be taken over a period of about two years (with intermissions) in bad cases; in addition to these, a thapsia plaster was sometimes ordered.

Upon examining the "Asthma Cure," I was at once convinced that it was the euphorbia pilulifera, and taking a sample of it over to Mr. Geo. E. Davis, the druggist who had obtained the euphorbia for me, and without informing him of my reason, asked him to compare the sample I had with his fluid extract of euphorbia pilulifera. This he did, and at once pronounced them the same. I then went back to Mr. A. with the two bottles, and he agreed that the taste, smell, and general appearance of the two were identical except that the fluid extract seemed less clear.

He had been taking thirty drops in a wineglassful of water after meals. He had not recognized it, as I had given it in combination with potassium iodide, potassium bromide, and tincture of belladonna. The third bottle was evidently nitrite of amyl in glycerine. His directions were to take thirty drops at the beginning of an acute attack and not to repeat it but once without consulting the "Institute." The odor was that of amyl nitrite. This, in the pamphlet, goes by the name of the "clincher."

It happened, oddly enough, that on going home that evening I found a new patient who was suffering from an acute attack of asthma, from which, he said, he had suffered since boyhood. This was on Saturday night, and I prescribed fluid extract of euphorbia pilulifera, thirty drops in a wineglassful of water every four hours, telling him to report to me the following Monday evening. I did not see him on Monday, but met him on Tuesday, when he said the reason he had not been around the night before was that the medicine had had such a wonderful effect that he had been able to go back to work. The patient told me a month afterward that he had never breathed so freely before in his life. He was a brakeman on the railroad, and was much exposed.

A third patient, a photographer, has given me the same brilliant results since then. I am fully convinced that the euphorbia pilulifera is the keynote to the undoubted and remarkable results obtained by the "Buffalo Asthmatic Institute" in the treatment of asthma. Only a few nights ago, a friend of large experience in practice told me that one of his own patients was under their care and that he is now able to sleep in a recum-

bent posture for the first time in months. My patient tells me the "Institute" has prospered to such a degree that it has opened offices in New York City, and that whenever he goes over he finds the offices filled with patients, and he says they all bear testimony to the wonderful good done them. The head of the affair is Dr. P. Harold Hayes, a graduate, I understand, of one of our leading schools. Now, of course, he gets his results by natural means, as it is not an age of miracles, and I feel confident that I have indicated above what his specific is.

I have learned that euphorbia pilulifera is a very common weed in Australia, and that it has a great local reputation there in the treatment of asthma and chronic bronchitis. Dr. J. P. Crozer Griffith very kindly sends me the following abstracts connected with the drug.

"W. Jayes, in the *Ceylon Med. Jour.*, Aug. 1888, describes the plant known in Sinhaleese as Boordada-Keeriya. The children use the juice to tattoo their arms. The author reports a case of asthma and one of chronic bronchitis, both very obstinate and of long standing, greatly relieved after a few doses of two fluid ounces of the decoction, taken three times a day. Thomas Christy in 'New Commercial Plants and Drugs' Nos. v and vii, 1888, gives an account of the plant and a history of its introduction into medicine. He says it was first used for asthma and other bronchial affections in Australia. He describes the method of making the decoction. I have now under my care an old lady with chronic bronchitis who is doing wonderfully well upon thirty drops of [the fluid extract of] euphorbia pilulifera, t.d."

I trust that this may be the means of stimulating the profession to using what the above experience has led me to feel may prove a specific for this most troublesome affection.

ADDENDUM

Having decided upon reprinting the above article in consequence of receiving many requests for copies of it, I desire to take this opportunity of adding a few notes of interest, gained by a further experience with euphorbia pilulifera.

First.—I have found that probably the most satisfactory method of exhibiting it is by giving thirty drops of the fluid extract in a wineglass of water every three hours. This masks the exceedingly acrid, pungent taste so much that I have found no trouble in administering it.

Second.—It should be used conscientiously and persistingly, with proper intermissions, for a long period of time, in many instances for two years or longer; as we possibly not only have some specific morbific agent to overcome, but also the element of habit—a factor I think too often lost sight of in the clinical handling of disease.

Third.—That a careful and strict control of the regimen and personal habits of the patient should be insisted upon at the outset; as I am con-

vinced that a large share of the unquestioned success of the Buffalo people is due to the fact that this concession on the part of the patient is made a *sine qua non*—the patient being obliged, for instance, to abstain from the use of tobacco, if that appears to be the exciting cause, or to modify the appetite if that be a source of disorder.

In my hands and in the cases I reported two years ago, the good results have been lasting and very satisfactory in every way, and I have personal knowledge of many cases cured by the Buffalo Institute.

A prominent Brooklyn physician in a recent letter to me, regarding the subject, uses the following expression, "Your article has been of untold value to me and to my patients."

This is very gratifying, as it leads me to hope that the large field of usefulness suggested by me for the drug may be realized by many others than myself.

In Memoriam

JULIAN COHN

It is with regret that we announce the death on November 9, 1954, of Julian Cohn, after a prolonged illness.

Dr. Cohn was born on September 30, 1892, in New York City, and attended high school there. He received his college education at the University of Texas, and his medical degree was awarded in 1924. He interned at Alameda County Hospital, California, and was licensed to practice in California and Texas. After taking postgraduate work in allergy in 1932 at the New York Hospital of Cornell Medical School, he limited his practice to allergy. Dr. Cohn was Assistant Professor of Clinical Medicine at the College of Medical Evangelists in Los Angeles, and was Chief of Allergy at the California Babies Hospital Clinic. He also served on the staffs of the California Lutheran Hospital, White Memorial Hospital, and French Hospital. He was a member of Phi Delta Epsilon, the American Medical Association, the California State Medical Society, and the San Francisco and Los Angeles County Medical Societies.

In 1946, Dr. Cohn was elected an Associate Fellow of the American College of Allergists, and due to his illness was placed on inactive status in January, 1954. His leisure time interests included nature and music.

Dr. Cohn is survived by his wife, Sally; two brothers, Max and Philip of New York City, and two sisters, Mrs. Birdie Michael of New York and Mrs. William Keith of Seattle, Washington, to whom the officers and members of the College extend their sincere sympathy.

News Items

SECOND INTERNATIONAL CONGRESS OF ALLERGOLOGY

The Second International Congress of Allergology will be held, by invitation of the Brazilian Allergy Society, in Rio de Janeiro, November 6-13, 1955, under the chairmanship of Dr. F. W. Wittich, Minneapolis, Minnesota, President of the International Association of Allergology. A wide and extensive program dealing with almost all important problems of allergy and related immunology, biochemistry, pharmacology and therapeutics has been elaborated, and is under preparation by the I.A.A. and the Brazilian Allergy Society.

Sir Henry H. Dale, London; Professor Pasteur Vallery-Radot, Paris; Professor Bernardo Houssay, Buenos Aires; and Dr. Robert Cooke, New York City, have been invited as guest speakers. The official languages will be English, French, and Spanish, and the main topics will be presented in these three languages, although scientific communications and discussions may be presented in the native language of the author.

The scope of the program is wide, including symposia on: Histamine, Its Metabolism and Its Role in Allergy; Histamine Liberators; Drug Allergy; Allergic and Toxic Reactions to Drugs; Hematologic Responses to Drugs; Cross Sensitizations; Chemistry of Antigens and Antibodies; Cellular Antibodies; Quantitative Immunological Techniques Applied to Allergy; Localization of Antibodies; Physiopathology of the Asthmatic Patient; Electrolytic Disturbances in Asthmatic Patients; Death Due to Asthma; Status Asthmaticus; Climatic Asthma; Hormonotherapy of Asthma; Hormones and Allergy; Allergy to Homologous Hormones; Antihistamine Substances; Specific and Nonspecific Treatments in Allergy; Psychosomatic Aspects of Allergy; Dermatologic Allergy; Industrial and Contact Dermatitis; Allergy to Animal Parasites; and Allergy to Microbial Organisms.

A limited number and a selection of scientific communications will be presented.

A very interesting program including scientific and technical exhibits, receptions, excursions, entertainments, banquets and also a ladies' program elaborated by the Brazilian Allergy Society will make of this Congress a never-to-be-forgotten meeting.

All information concerning the Congress is available from the General Secretary of the I.A.A., Dr. Bernard N. Halpern, 197 Boulevard Saint Germain, Paris (7o), France, or from the Secretary of the Sociedade Brasileira de Algeria, Dr. Fabiano Alves, Avenida Rio Branco 277, 7o Andar. Sala 705, Rio de Janeiro, Brazil.

A Newsletter especially for North Americans planning to attend the congress will soon be sent out by Dr. Fred W. Wittich, president, 423 LaSalle Building, Minneapolis, Minnesota. Those from North America wishing to participate in the program should send copies of their manuscripts in triplicate to Dr. Wittich not later than July 31, 1955.

AMERICAN FOUNDATION SPEAKERS BUREAU

The New York Allergy Society and the American Foundation for Allergic Diseases are collaborating in establishing a speakers bureau, under the chairmanship of Dr. Paul F. deGara, an Active Fellow of the College. Several College members have already participated in this activity. Dr. deGara spoke on November 17, 1954, at the Judson Health Center, New York City, on "Allergy in Infants: Atopic Eczema." On November 30, 1954, Dr. Harold Abramson addressed the Auxiliary of Rockaway Beach Hospital on the subject "Behavior Problems of the Allergic Child." Through this combined service talks on problems of allergic diseases by specialists in allergy are available to clubs, schools and professional groups in the New York area, without charge. Dr. Susan Dees of Duke University Hospital spoke on "Pediatric Allergy" over WTPC in Washington, D. C., November 1, 1954.

NEWS ITEMS

NOTICE OF ELECTION OF OFFICERS AND REGENTS

Article V, Section 7(g) of the Bylaws of The American College of Allergists entitled "Nomination of Officers," as amended at the annual meeting of the Board of Regents held in Miami Beach on April 4, 1954, reads as follows:

"The Nominating Committee shall be composed of five (5) members: The President, two (2) members of the Board of Regents each of whom has served at least two (2) years on the Board, and two (2) past Presidents, both Regents and past Presidents to be selected by the Board. Not earlier than three (3) months, but not more than six (6) months after its selection the Nominating Committee shall pick one (1) candidate for each elective office and this shall be known as the official ballot. In making its selection it shall take into consideration the qualifications, fitness, capacity, standing and accomplishments in the field of allergy of those considered for selection, and all information contained in the membership records maintained in the Secretary's office as to any proposed selectees shall be seasonably supplied to the Committee for this purpose. The Nominating Committee shall report its selections to the Secretary-Treasurer's office and as soon as convenient thereafter, but not less than three (3) months before the ensuing election, notice of this official ballot shall be given to all voting Fellows of the College. This notice may be given either by publication thereof in the official organ of the College, ANNALS OF ALLERGY, or by mail. Additional nominations may also be made by petition, signed by ten (10) Fellows and sent to the office of the Secretary-Treasurer, provided said additional nominations are received in the office of the Secretary-Treasurer at least thirty (30) days prior to the next annual meeting. Nominations may also be made from the floor at any annual meeting. The election of officers and Regents shall be by ballot and shall be by a majority of the votes cast at the annual meeting."

The present Nominating Committee consists of Drs. Homer E. Prince, Chairman, Hal M. Davison, J. Warrick Thomas, Harry S. Bernton and L. Everett Seyler.

This Committee selected one candidate for each elective office and reported its selections, which constitute the official ballot, to the Secretary's office in a letter dated January 28, 1955, delivered January 31, 1955. Thereafter, an emergency session of the Nominating Committee was held in New York, at which time the official ballot previously reported to the Secretary-Treasurer's office was slightly modified. This change was reported in a telegram received from Dr. Prince, Committee Chairman, on February 11, 1955. The slate, as finally selected, appears below:

President-Elect ..... ETHAN ALLAN BROWN, M.D.
First Vice President ..... JOHN D. GILLASPIE, M.D.
Second Vice President ..... A. M. TARGOW, M.D.
Secretary-Treasurer ..... FRED W. WITTICH, M.D.
Board of Regents (Three-Year Term) ..... S. H. JAROS, M.D.
MAURICE S. SEGAL, M.D.
DAVID R. THOMAS, JR., M.D.

AMERICAN ACADEMY OF ALLERGY

At the annual business meeting of the American Academy of Allergy, held at the Statler Hotel, New York, February 8, 1955, the following were elected as officers for the coming year:

President—Dr. Stanley F. Hampton, St. Louis, Mo.
President-Elect—Dr. Carl E. Arbesman, Buffalo, N. Y.
Vice President—Dr. Abraham Colmes, Boston, Mass.
Secretary—Dr. Francis C. Lowell, Boston, Mass.
Treasurer—Dr. Max Samter, Chicago, Illinois
Historian—Dr. Homer Howes, Detroit, Mich.
Member of the Executive Committee—Dr. Bram Rose, Montreal, Canada

NEWS ITEMS

SECOND NATIONAL CONGRESS OF ALLERGY OF THE ITALIAN SOCIETY OF ALLERGY

The Second National Congress of Allergy, sponsored by the Italian Society of Allergy (Società Italiana di Allergologia), took place in Naples on December 19-20, 1954. Prominent scientists in attendance report a very successful meeting. The proceedings of the congress will appear shortly in *Folia Allergologica.* At this meeting the board of directors of the Italian Society of Allergy was confirmed with the same list of members.

ARGENTINE ASSOCIATION OF ALLERGY

At an Assembly held December 1, 1954, the Argentine Association of Allergy elected the following officers: President, Dr. Guido Ruiz Moreno; Vice President, Dr. Alois E. Bachmann; Secretary, Dr. Miguel Agustin Solari; Alternate Secretary, Dr. Heriberto H. Minsk; Treasurer, Dr. Andres Martinez Marchetti; Alternate Treasurer, Dr. Jóse F. Dumm; Voters, Drs. Leon Bentolila, Eduardo Lopez Lacarrere, Lorenzo Giscafre, Jose Martorelli, and Salvador Pisani.

CUBAN ALLERGY SOCIETY

The following officers have been elected by the Cuban Allergy Society to serve for the coming year: President, G. Estrada de la Riva, M.D.; Vice President, José Cadrecha, M.D.; Secretary, José Quintero Fossas, M.D.; Treasurer, Julio de los Santos, M.D.; Members-at-Large, José Pedrera, M.D., Josefina Amiguet, M.D., and Javier Fernandez de Castro, M.D.

SWEDISH ASSOCIATION OF ALLERGOLOGY

The Swedish Association of Allergology met on Monday, November 15, 1954, at Caroline Hospital in Stockholm. The program consisted of the following lectures: "Studies of Therapeutic Vaccine in Cases of Bronchial Asthma" by G. Bergquist; "Some Cases of Excessive Hypersensitivity to Staphylococcic Vaccine" by A. Nilzen; "Some Historical Viewpoints on the Development of Allergology" by H. Colldahl; "Some Experiments of Sulphur Treatment in the Case of Bronchial Asthma" by P. O. Osterman; and "Meat Allergy" by S. Kraepelin.

POSTGRADUATE COURSE IN ALLERGY

A postgraduate course in allergy on the "Modern Management of Allergic Diseases" will be given at The Institute of Allergy of The Roosevelt Hospital, New York City, from May 9-20, 1955. The fee for the course is $150.00. Enrollment is limited, and those desiring information should write to Dr. Robert A. Cooke, 428 West 59th Street, New York 19, N. Y.

POSTGRADUATE COURSE ON DISEASES OF THE CHEST

The eighth annual Postgraduate Course on Diseases of the Chest, under the sponsorship of the American College of Chest Physicians, will be held March 7 to 11, 1955, at the Bellevue-Stratford Hotel, Philadelphia, Pennsylvania. The fee for the course is $75.00. Further information and registration may be obtained through the American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

POSTGRADUATE CONTINUATION COURSES FOR PHYSICIANS

The Council on Medical Education and Hospitals of the American Medical Association has compiled and published on pages 1429-1477 of the December 11, 1954, issue of *The Journal of the American Medical Association*, a list of the postgraduate continuation courses for physicians for the period January 1, 1955 to September 1, 1955. The approved postgraduate courses in allergy are given as follows:

Institution	*Title of Course*	*Schedule of Course*	*Fee*
Baltimore City Medical Society, 1211 Cathedral St., Baltimore	Postgraduate Refresher Course	March 3-30, once weekly, part time	None
Cook County Graduate School of Medicine, 707 S. Wood Street, Chicago	Allergy & Related Conditions	March 23, 10 days, part time	$125.00
	Personal Course in Allergy	Arranged, 6 mo., first of every month, full time	$500.00
	Personal Course in Allergy	Arranged, 6 mo., first of every month, full time	$200.00
American College of Allergists, 401 LaSalle Bldg., Minneapolis. At: Morrison Hotel, Chicago	11th Annual Graduate Instructional Course in Allergy	April 25-27, full time	$ 50.00
University of Minnesota, Center for Continuation Study, Minneapolis	Allergy & Chest Diseases for General Practitioners	April 18-20, full time	$ 25.00
Joint Committee on Postgraduate Education, 1313 Bedford Ave., Brooklyn, N. Y. At: Beth-El Hospital	Allergy	April, 10 weeks, part time	$ 30.00
University of Buffalo School of Medicine, 3435 Main St., Buffalo	Allergy	March 2-3, full time	$ 25.00
New York Medical College, Flower & Fifth Avenue Hospitals, 1 East 105th St., New York	Allergy (dm 1096)	Arranged, 2 months, full time	$ 50.00
New York Polyclinic Medical School & Hospital, 345 W. 50th St., New York	Allergy	Arranged, twice weekly, part time	$ 50.00
New York University-Bellevue Medical Center, 550 First Ave., New York	5416-A Refresher Course in Allergic Conditions	March 14-16, full time	$ 50.00
	543-A Allergy	April 15-June 3, part time	$ 40.00
University of Pittsburgh School of Medicine, 3941 O'Hara Street, Pittsburgh. At: Montefiore Hospital	Allergy in Practice	May 9-13, full time	$ 50.00
American Academy of Allergy, 208 E. Wisconsin Ave., Milwaukee, Wis. At: Roosevelt Hospital, New York Hospital, Mt. Sinai Hospital, New York City	American Academy of Allergy Postgraduate Clinics	February 4-6, full time	None

ADVISORY BOARD FOR MEDICAL SPECIALTIES

In response to requests for the names of the various Advisory Boards for the Medical Specialties and their members, the present list is herewith submitted:

Association of Medical Colleges	
William S. Middleton, M.D.	University of Wisconsin Medical School, Madison, Wisconsin
Stanley E. Dorst, M.D.*	University of Cincinnati, Cincinnati, Ohio
The American Hospital Association	
Frank R. Bradley, M.D.	Barnes Hospital, St. Louis, Mo.
Robin C. Buerki, M.D.*	Henry Ford Hospital, Detroit 2, Mich.
The Federation of State Medical Board of the U.S.A.	
Creighton Barker, M.D.	160 St. Ronan Street, New Haven, Conn.
Walter L. Bierring, M.D.*	406 Sixth Avenue, Des Moines, Iowa
The National Board of Medical Examiners	
Robert A. Moore, M.D.	Office of Vice Chancellor, University of Pittsburgh, Pittsburgh, Pennsylvania
John P. Hubbard*	University of Pennsylvania Medical School, Philadelphia, Pennsylvania
The American Board of Ophthalmology	
William L. Benedict, M.D.	100 First Avenue S.W., Rochester Minn.
Edwin P. Dunphy, M.D.*	243 Charles Street, Boston, Mass.
The American Board of Otolaryngology	
Frederick T. Hill, M.D.	177 Main Street, Waterville, Maine
Dean M. Lierle, M.D.*	University Hospitals, Iowa City, Iowa
The American Board of Obstetrics and Gynecology	
Herbert E. Schmitz, M.D.	25 E. Washington, Chicago, Illinois
Robert L. Faulkner, M.D.*	2105 Adelbert Road, Cleveland, Ohio
The American Board of Dermatology and Syphilology	
Nelson Paul Anderson, M.D.	2007 Wilshire Blvd., Los Angeles 5, California
Anthony C. Cipollaro, M.D.*	40 East 61st St., New York 21, N. Y.
The American Board of Pediatrics	
Lee Forrest Hill, M.D.	604 Locust Street, Des Moines, Iowa
John M. K. Mitchell*	6 Cushman Road, Rosemont, Pa.
The American Board of Psychiatry and Neurology	
Bernard J. Alpers, M.D.	111 North 49th St., Philadelphia, Pa.
Francis Gerty, M.D.	912 South Wood St., Chicago 12, Ill.
David A. Boyd, Jr., M.D.†	Mayo Clinic, Rochester, Minnesota
The American Board of Radiology	
H. Dabney Kerr, M.D.	University Hospital, Iowa City, Iowa
B. R. Kirklin, M.D.*	Mayo Clinic, Rochester, Minnesota
The American Board of Orthopedic Surgery	
Clarence H. Heyman, M.D.	10515 Carnegie Ave., Cleveland 6, Ohio
Harold A. Sofield, M.D.*	122 South Michigan Ave., Chicago, Ill.
The American Board of Urology	
Rubin Flocks, M.D.	University Hospital, Iowa City, Iowa
Harry Culver, M.D.*	6740 Oglesby Avenue, Chicago, Illinois

*Corresponding Member.

†Secretary-Treasurer of Board to whom correspondence should be directed.

The American Board of Internal Medicine	
Walter L. Palmer, M.D.	950 East 59th St., Chicago, Illinois
Henry M. Thomas, Jr., M.D.*	1201 N. Calvert St., Baltimore 2, Md.
William A. Werrell, M.D.†	1 West Main Street, Madison, Wisconsin
The American Board of Pathology	
William B. Wartman, M.D.*	303 East Chicago Avenue, Chicago, Ill.
The American Board of Surgery	
Walter G. Maddock, M.D.	250 E. Superior St., Chicago, Illinois
John B. Flick, M.D.*	225 S. 15th St., Philadelphia, Pa.
The American Board of Anesthesiology	
R. J. Whitacre, M.D.	Huron Road Hospital, E. Cleveland, Ohio
Curtiss B. Hickcox, M.D.*	Hartford Hospital, Hartford, Conn.
The American Board of Plastic Surgery	
W. H. Steffensen, M.D.	1810 Wealthy St. S.E., Grand Rapids, Mich.
Bradford Cannon, M.D.	330 Dartmouth St., Boston, Mass.
The American Board of Neurological Surgery	
Francis C. Grant, M.D.	3400 Spruce St., Philadelphia, Pa.
Leonard T. Furlow, M.D.*	3720 Washington Ave., St. Louis 8, Mo.
The American Board of Physical Medicine & Rehabilitation	
Robert L. Bennett, M.D.	Warm Springs Foundation, Warm Springs, Georgia
Earl C. Elkins, M.D.*	Mayo Clinic, Rochester, Minnesota
The American Board of Preventive Medicine & Public Health	
William P. Shepard, M.D.	2330 Clay Street, San Francisco 15, Cal.
Ernest L. Stebbins, M.D.*	Johns Hopkins Univer., Baltimore, Md.
The American Board of Proctology	
Walter A. Fansler, M.D.	1829 Med. Arts Bldg., Minneapolis, Minn.
Louis A. Buie, M.D.*	Mayo Clinic, Rochester, Minnesota

TRAVELING LECTURESHIP ON MEDICAL WRITING INAUGURATED

Dr. Jacques P. Gray of Detroit, Michigan, Director of Special Medical Services and Medical Consultant of Parke, Davis & Co., has been appointed by the Board of Directors of the American Medical Writers' Association as its volunteer Visiting Lecturer on Medical Writing for the year 1955. Under the auspices of the Educational Committee of the Association, Dr. Gray will give lectures on medical writing to medical undergraduates and to interns and residents of teaching hospitals in connection with the medical schools of the United States and Canada. He will also be available for talks on medical writing before other medical groups as his teaching schedule permits. Parke, Davis & Company of Detroit, Michigan, is bearing the entire expense of this pioneer educational work.

LOS ANGELES ALLERGY SOCIETY

At the January 29, 1955 meeting of the Los Angeles Allergy Society the following men were elected to serve as officers for the coming year:

President.....Walter MacLaren, M.D.
Vice President.....A. M. Targow, M.D.
Secretary-Treasurer.....D. Edward Frank, M.D.

SOUTHEASTERN ALLERGY FORUM

The annual meeting of the Southeastern Allergy Forum, which will be held March 25 and 26 at the Orange Court Hotel in Orlando, Florida, will have as its theme "Allergy and Its Relation to Industrial Medicine." Speakers will include Dr. Stanley Hampton, president-elect of the American Academy of Allergy; Dr. Lawrence J. Halpin, president-elect of the American College of Allergists; and Dr. E. M. Gunn, medical director of Sonoco Products, Hartsville, South Carolina. Further details about this meeting may be obtained from the secretary, Dr. Katherine B. MacInnis, 1515 Bull Street, Columbia, South Carolina.

AERO MEDICAL ASSOCIATION MEETING

The twenty-sixth annual meeting of the Aero Medical Association will be held from March 20 through March 23 at the Hotel Statler, in Washington, D. C. General Otis O. Benson, Jr., of the U. S. Air Force Medical Service, and head of the association, announced that medical people from many countries will attend and participate in the presentation of scientific reports on aviation medicine. The association, organized in 1929, has as one of its primary aims the promotion of safety in aviation, and the organization now exercises international influence in stimulating the science and art of aviation medicine. One afternoon's program will be devoted to a special session on space medicine.

NEWS OF MEMBERS

Dr. M. Murray Peshkin, New York City, has been appointed Professor of Clinical Medicine (Allergy) and Professor of Clinical Pediatrics (Allergy) at the newly-organized Einstein College of Medicine at Yeshiva University.

Dr. Boen Swinny, Consultant in Allergy at the Robert B. Green Hospital and the Brooke General Hospital, San Antonio, Texas, and Dr. Leon Unger, Associate Professor of Medicine at Northwestern University Medical School, Chicago, Illinois, have been elected as Medical Trustees of the American Foundation for Allergic Diseases.

On January 1, 1955, the journal *Antibiotics and Chemotherapy* was divided into two separate publications, one dealing with the experimental phase and the other with the clinical aspects of research in antibiotic agents. Dr. Ethan Allan Brown, Editor of the ANNALS OF ALLERGY, has been appointed to the Editorial Board of the new journal.

Mayer A. Green of Pittsburgh, Pennsylvania, an Active Fellow of the College, was awarded the Certificate of Merit by the Pennsylvania Allergy Society at its Fall meeting in Altoona, Pennsylvania, in recognition of excellent and outstanding work in the field of allergy during the year 1953-54.

Dr. Kenneth Craft of Indianapolis, Indiana, Chairman of the Otolaryngologic Allergy Committee of the College, will read a paper entitled "Diagnosis of Nasal Allergy" at the meeting of the American Medical Association to be held in Atlantic City, June 9, 1955.

MESSAGE TO THE WIVES OF OUR COLLEGE MEMBERS, SUSTAINING MEMBERS AND HONORARY MEMBERS

On April 8, 1954, the Women's Auxiliary of The American College of Allergists, Inc., was formed. Membership applications were sent to all of the wives, and the response has been wonderful. Charter Membership is limited to those joining within one year from date of organization, and to date we have 174 Charter Members.

We are inserting this note in the ANNALS, as a reminder that only two months remain in which to become a Charter Member. If you have overlooked or misplaced your application, you may use the one on this page.

The initial fee for becoming a member is five dollars ($5.00), and the annual dues is five dollars ($5.00), both payable in advance. Complete the application, detach, enclose your check for ten dollars ($10.00) made payable to Women's Auxiliary, American College of Allergists, Inc., Eunice Swinny, Treasurer, and send to Mrs. Boen Swinny, 143 Bluebonnet Blvd., San Antonio 9, Texas.

MRS. J. WARRICK THOMAS
Secretary

MRS. MORRIS A. KAPLAN
President

Application for Membership

DATE.....

NAME .....

MAIDEN NAME .....

HOME ADDRESS .....

CITY .....ZONE....STATE .....

BOOK REVIEWS

THE KIDNEY. Ciba Foundation Symposium. By A. A. G. Lewis, M.D., and G E. W. Wolstenholme, Editors, assisted by Joan Etherington. 333 pages. Price $6.75. Boston: Little, Brown and Company, 1954.

The Ciba Foundation in London, in collaboration with the Renal Association, arranged a symposium on "The Kidney" in London in July, 1953. The papers presented by the thirty-five participants at this session are printed in full in this volume, together with discussion. The participating members represented Great Britain, Belgium, Holland, Denmark, France, Sweden, Switzerland, and the United States, and were selected for their contributions in the fields of renal anatomy, physiology, pathology, and medicine. The papers cover various aspects of structural and functional relationships in the kidney, regulation of the acid-base balance, tubular functions other than the regulation of acid-base balance, general problems of electrolyte excretion, and the renal share in the volume control of body fluid. This volume will be valuable to those especially interested in the kidney and its functions and also to those interested in the larger field of acid-base balance and regulation of body water.—V. S.

HYPERTENSION: HUMORAL AND NEUROGENIC FACTORS. Ciba Foundation Symposium. By G. E. W. Wolstenholme and Margaret P. Cameron, Editors, assisted by Joan Etherington. 294 pages, illus. Price $6.75. Boston: Little, Brown and Company, 1954.

This little volume represents the pooling of knowledge and ideas on the subject of hypertension among a panel of thirty-three well-known authorities in the field of hypertension research. The twenty-one papers included here, and the discussion which follows each, comprise the Ciba Foundation Symposium on Hypertension: Humoral and Neurogenic Factors. The problem of hypertension and its effect on the cardiovascular system is discussed here from the point of view of applied physiology. The papers deal largely with the basic problems of blood pressure control and the mechanisms producing experimental hypertension, but also cover the causes and therapy of clinical hypertension. Although the book is not intended as a clinical review nor as a guide to therapy, it will be of interest to clinicians, biochemists, pharmacologists and physiologists.—V. E. S.

REACTIONS WITH DRUG THERAPY. Harry L. Alexander, M.D., Emeritus Professor of Clinical Medicine, Washington University Medical School, St. Louis, Missouri. 301 pages, illus. Philadelphia: W. B. Saunders Co., 1955. Price $7.50.

With the incidence of drug reactions reaching alarming proportions, Dr. Alexander's book is both timely and necessary. From the multitudinous literature on this subject, the author has compiled a helpful guide to enable the physician to understand the reactions of the hypersensitive patient.

This book does not deal with the toxic effects of overdosage nor with the expected pharmacologic reactions, but rather with the lesions of hypersensitivity (skin eruptions, blood dyscrasias, fever, and shock) in which drugs are the etiologic agent. The author points out that reactions to drugs fall into definite clinical patterns, and several mechanisms may cause them. He uses the term "hypersensitivity" to cover the underlying process, which he discusses in Chapter I. In the second chapter he examines the mechanisms of hypersensitivity, dealing with

the allergic mechanism, antigen, antibody, and desensitization. Chapters III and IV list the various drugs found to produce reactions, divided into dermatologic manifestations and systemic patterns. Chapters V, VI, and VII cover the anti-infectious drugs, subdivided into chemotherapeutic preparations, antibiotic preparations, and the drugs used in tuberculosis. Subsequent chapters are concerned with anti-arthritic drugs, sedative drugs, drugs used in cardiovascular disorders, antithyroid drugs, antihistamine drugs, organ extracts, vitamins, serums and vaccines, plant products, local anesthetics, and miscellaneous drugs. Each chapter is followed by a list of references.

Nineteen tables are included, the first showing the concentrations of some common drugs used for patch tests, followed by seventeen tables listing drugs causing the various conditions, and the last table summarizing the comparatively few drugs responsible for the most common reactions.

Aided by this volume the physician will know how other patients have reacted to a given drug, whether there is any record of fatality from its use, whether it is often or rarely accompanied by a reaction, what the mechanism of the reaction and course of action is likely to be, and what measures, other than mere discontinuance of the drug, are indicated. A working knowledge of the various drugs and their reactions can be obtained readily from study of this volume.—V.E.S.

DISEASES OF THE SKIN FOR PRACTITIONERS AND STUDENTS. George Clinton Andrews, M.D., Clinical Professor of Dermatology, Columbia University College of Physicians and Surgeons, New York, N. Y. Fourth edition. 877 pages. Philadelphia: W. B. Saunders Company, 1954. Price $13.00.

Increased knowledge of many dermatologic conditions in the last eight years has made another revision of this book necessary. The new edition places greater emphasis on the histopathology of the skin, contains enlarged and expanded chapters on viral and fungus diseases and a revamped chapter on syphilis in the light of radical new treatment. New diseases and symptom-complexes have been added to this edition, and new discussions have been written on lupus erythematosus, skin manifestations of internal cancer, diagnosis and treatment of the various types of pigmented nevi and the relationship of the junctional nevus to melanoma. Significant changes have been made in the chapters on tumors in the light of expanding knowledge. In addition, every sentence has been carefully scrutinized and revised in detail so that the entire text reflects the latest information. Discussion of each disease is followed by the latest and most effective forms of treatment, many given by the author himself.

This is actually a dermatologic atlas containing 777 illustrations, providing a firm foundation in academic dermatology and the latest methods of management and treatment. For the student, the general practitioner, the surgeon, the industrial physician, and the dermatologist this book is invaluable.—V.E.S.

PERIPHERAL VASCULAR DISEASES. Second Edition. Edgar V. Allen, M.D., Nelson W. Barker, M.D., and Edgar A. Hines, Jr., M.D., Section of Medicine, Mayo Clinic; Professors of Medicine, Mayo Foundation, Graduate School, University of Minnesota; with Associates in the Mayo Clinic and Mayo Foundation. 825 pages. Philadelphia: W. B. Saunders Co., 1955. Price $13.00.

The second edition of this Mayo Clinic book is now based on more than thirty years' firsthand experience of a number of experts in the field of peripheral vascular diseases, based on cases seen and treated at the Mayo Clinic.

In this rapidly expanding field of medical science, there are many controversial points which the authors have covered, although expressing definitely their own

opinions. The subject of hypertension has been omitted, as there is much controversy about it and whole books have been written on the subject; likewise, vascular diseases of the central nervous system, involving considerations of neurology, and vascular diseases of certain viscera linked with other diseases, have been omitted.

This revision presents a number of entirely new subjects; aortography, coarctation of the aorta, purpura, hypertensive ischemic ulcers of the leg, techniques of sympathectomy, non-vascular operation for intermittent claudication, and surgical treatment of varices, aortic aneurysms, and vascular injuries. The section on anticoagulants has been entirely rewritten and a whole chapter is devoted to varicose veins.

Diseases of all blood vessels outside of the heart and central nervous system are covered in this manual. The sections on medical and surgical treatment comprise almost 200 pages of the latest methods of treatment for a number of peripheral vascular disorders. There are 316 helpful illustrations.—V.E.S.

REGIONAL ALLERGY OF THE UNITED STATES, CANADA, MEXICO AND CUBA. A Symposium of Thirty-nine Contributors. Edited by Max Samter, M.D., Chief, Allergy Clinic, Research and Educational Hospitals, Associate Professor of Medicine, University of Illinois, College of Medicine, Chicago, Illinois; and Oren C. Durham, Lecturer in Allergy with rank of Assistant Professor, University of Illinois, College of Medicine, Chicago, Illinois, and Chief Botanist, Abbott Laboratories, North Chicago, Illinois. 395 pages. Springfield, Illinois: Charles C Thomas, Publisher, 1955. Price $8.50.

This monograph in the American Lecture Series represents an attempt to provide a comprehensive and useful survey of the local allergic problems of the United States, Canada, Alaska, Mexico, and Cuba.

In recent years, the population of the United States has become a mobile population, due to the ease of modern travel, early retirement age, rapid expansion of industrial development and the trend toward dispersion. A large percentage of our citizens are on the move at some time during a given year. Since many of these people have allergies of various sorts, the new environment into which they go or through which they pass will present hazards to their well-being if they do not know its allergic potential. This volume is designed to help these people and their physicians and counsellors, both medical and nonmedical, anticipate their allergic future in a new area.

The book is divided into three general sections, dealing with the eastern, central, and western sections of the area under discussion. These areas are in turn subdivided into states or groups of states, and thirty-nine well-known practicing allergists have written of the geography, climate, and allergenic factors in the area in which they practice. These chapters also contain valuable data on prevailing winds and weather, dispersal of pollen and mold spores, pollen incidence, contaminants of various kinds, occupations and industries, vegetation, social and educational facilities, and allergic factors peculiar to the region. A section on nomenclature attempts to bring together the various local and botanical names of the types of vegetation discussed, and an appendix contains a ragweed pollen index for the United States and adjacent areas, revised to March, 1954.

For the first time, it is possible to obtain information in one place on the allergic hazards, potential, and control measures of a given area in the United States and neighboring countries. The demand for this book, the first of its kind, is increasing as its significance is appreciated.—V.E.S.

REPRODUCTIVE SYSTEM. Frank H. Netter, M.D. Volume II, Ciba Collection of Medical Illustrations. 286 pages, 233 illustrations. Summit, New Jersey: Ciba Pharmaceutical Products, Inc., 1954.

This book, which is Volume II in the Ciba Collection of Medical Illustrations, is composed of 233 paintings of the normal and pathologic anatomy of the male and female reproductive systems, eighty-nine of which appear in print for the first time. The author, Dr. Frank H. Netter, is a physician as well as an outstanding artist.

The first three plates of the book are devoted to the development of the genital tracts and functional relationships of the gonads, followed by a section containing eighteen plates on the normal anatomy of the male genital tract and three sections, comprised of fifty-five plates, on the diseases of the various organs of the male genital tract. Two-thirds of the book is devoted to the female genital tract, with thirty-one colored plates and text describing the normal anatomy and its functional relationships, followed by five sections with seventy-eight plates on the diseases of the various organs. Twenty-five plates and text comprise a section on pregnancy and its diseases, and nineteen plates show the anatomy and pathology of the mammary gland. The last section of four plates deals with the intersexes.

About half of each page is devoted to the colored plates and the rest to the explanatory text which is brief and complete. The emphasis is on anatomy, physiology, embryology, and pathology, although diagnostic procedures are described and illustrated and therapy is restricted to a few general directions. The book is not intended as a complete and comprehensive textbook, but rather as a pictorial and verbal close-up of the most important pathologic conditions of the reproductive system. The text is easily understandable, the plates are beautifully executed and reproduced, and the format is attractive. Dr. Netter was assisted in this presentation by a number of collaborators who are named at the beginning of each section. The plates are followed by thirteen pages of index and a short list of references.

The volume is in reality a postgraduate course in male and female reproductive anatomy, physiology, and pathology.